

REMARKS

In the Final Office Action dated October 26, 2006 and the Advisory Action dated February 1, 2007, Claims 38 and 42-45 are pending and under examination. Claims 38, 42-43 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Liu et al. (*J. Inorganic Biochemistry* 1998 Vol. 71, page 1-6) in view of Pisanti et al. (*Marine Pollution Bull* (1988) Vol. 19, page 328-333). Claims 44-45 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Liu et al. in view of Pisanti et al. and further in view of Gold et al. (U.S. Patent No. 6,242,246).

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

At the outset, Applicants, through the undersigned, wish to thank Examiner Changhwa J. Cheu for the courtesy and assistance extended to Applicants during telephonic interviews conducted on April 23 and June 13, 2007.

In the Amendment filed June 14, 2007, Applicants amended Claims 38 and 44, and added Claims 46 and 47. In particular, Claim 38 as presently recited, further delineates that the toxicant is a metal atom in an aquatic, terrestrial, gaseous or industrial environmental sample. Applicants will now address each of the rejections in the Final Action.

Claims 38 and 42-43 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Liu et al. (*J. Inorganic Biochemistry* Vol. 71, pages 1-6, 1998) in view of Pisanti et al. (*Marine Pollution Bull* Vol. 19, pages 328-33, 1988).

The Examiner alleges that Liu et al. teach a method of measuring fluorescence quenching of DNA bound fluorescence dye, e.g., increasing dissociation or inhibition of

fluorescent dye bound to the DNA, by a sample containing copper (II) macrocyclic complexes. The Examiner states that Liu et al. teach that the presence of a copper (II) metal macrocyclic complexes would compete with binding the DNA molecule intercalated with the fluorescence ethidium dye. The Examiner contends that the binding constant of the copper is around 10^{-10} (M^{-1}), which falls within the micromolar range as claimed.

The Examiner acknowledges that Liu et al. do not explicitly teach detecting the inhibition or dissociation of the dye on the DNA as an indication of the presence of a metal. However, the Examiner alleges that Pisanti et al. teach that the presence of metals in the ecosystem, e.g., ocean or rivers, is of great concern because of the potential to impact the quality and physiology of marine organisms. The Examiner contends that Pisanti et al. teach that metal levels, such as copper, are essential for the biological equilibrium of the marine ecosystem.

Therefore, the Examiner alleges that it would have been obvious to one skilled in the art, at the time the present invention was made, to combine the teachings of Liu et al. and Pisanti et al. in order to measure the presence of copper in an aquatic sample.

Applicants respectfully submit that Claim 38, as amended, is directed to a method for detecting the presence of micromolar amounts of a toxicant in an aquatic, terrestrial, gaseous or industrial environmental sample, in which the toxicant is a metal atom, i.e., a metal toxicant that is free of any macrocyclic compound.

Applicants observe that according to Liu et al., each copper (II) macrocyclic complex contains a metal atom, i.e. copper (II). See Fig. 1. of Liu et al. The metal atoms (copper (II)) described in Liu et al. are not free of any macrocyclic compound. Liu et al.'s method requires an initial step of preparing and purifying copper (II) macrocyclic complexes (CuL) (see Fig. 1 and page 2, column 2, lines 2-5). Applicants respectfully submit that contrasting to the present

invention, Liu et al. do not disclose or suggest how to directly detect a metal atom that exists in an environmental sample in the absence of any macrocyclic compound.

Applicants submit that the macrocyclic complexes disclosed in Liu et al. are complexes between copper and either one of the two organic ligand (polypyridyl) compounds, L1 and L2. Applicants submit that in addition to copper, polypyridyl macrocyclic complexes may form with Fe, Co, Ni and Zn. See Truex and Holm, *Journal of the American Chemical Society* 94(13): 4529-4538 (1972) (copy attached hereto as **Exhibit A**, which is also cited by Liu et al.). Applicants respectfully direct the Examiner's attention to the fact that the stability of the complex between metal and macrocyclic polypyridyl is very strong. See Bazzicalupi et al., *Dalton Trans.* 591-597 (2004) (copy attached hereto as **Exhibit B**), in which the stability constant K_a of complexes between Hg, Cd and Zn and similar microcyclic compounds was calculated to be in the order of 10^{-16} M.

Applicants observe that Liu et al. disclose the displacement of ethidium bromide from DNA by a copper-polypyridyl complex, leading to fluorescence quenching. As a result of the high affinity of the macrocyclic compound for metals and the high affinity of the macrocyclic compound-metal complex for DNA, the method of Liu et al. is very sensitive and will detect very low, nontoxic levels of metals. Applicants submit that the high sensitivity of Liu et al.'s assay is afforded by the high affinity of the macrocyclic metal complexes for DNA resulting in a greater ability of the complexes to inhibit the DNA-dye interaction when compared to free metal ions.

In contrast, the present invention is directed to detecting a toxicant that is a metal in an environmental sample, i.e., metals that exist in an environmental sample at toxic levels. Applicants respectfully submit that contrasting to the method of Liu et al., the instantly claimed

method, which does not employ any macrocyclic compound, is more discriminating so that low or non-toxic levels of metal ions are not detected. Indeed, Applicants respectfully submit that in the context of a test for toxicants in environmental samples, the method of Liu et al. would be useless because of its ability to detect very low (non-toxic) levels of toxicants, leading to false positive results.

Applicants further submit that an analysis of the obviousness is governed by the Supreme Court's recent decision in *KSR Int'l Co. v. Teleflex Inc.* (550 U.S. ___, 2007 WL 1237837 (2007)). The *KSR* Court held that the Teaching, Suggestion or Motivation (TSM) test shouldn't be applied rigidly. However, the Court acknowledges that the TSM test still provides a helpful insight to the obviousness question. *Id.*, at 15. In addition, with respect to a combination of patents, the Court indicates that an invention is not obvious if the combination of old elements is not a predictable use of these elements according to their established functions giving predictable results. See, e.g., *Id.*, at 13 (emphasis added). The *KSR* Court also upheld the use of the "teaches away" argument to disprove obviousness. See, e.g., *Id.*, at 12.

In a MEMORANDUM issued by the Patent Office dated May 3, 2007 (copy attached hereto as **Exhibit C**), relating to the *KSR* decision, the Patent Office states that "in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Emphasis added.

In this regard, Applicants respectfully submit that the Examiner fails to identify any reason why one skilled in the art would modify the methods of Liu et al. by eliminating the use of a macrocyclic compound and to detect the presence of a metal ion directly in an environmental sample.

Applicants further respectfully submit that even assuming, *arguendo*, that one skilled in the art would have been motivated to eliminate the use of a macrocyclic compound, Liu et al. would not have provided a reasonable expectation of success, or any predictability, that micromolar amounts of a toxicant, independent of a macrocyclic compound, can be detected directly by employing a nucleic acid intercalated with a dye. As discussed above, Liu et al.'s method would simply not work for the intended purpose of the present invention.

Furthermore, the secondary reference to Pisanti et al. merely teach that the presence of metals in the ecosystem is of great concern and that metal levels are essential for the biological equilibrium of the ecosystem. Applicants submit that this reference does not obviate the deficiencies of the primary reference to Liu et al.

In view of the foregoing, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness under *KSR*. Applicants respectfully submit that the presently claimed methods are not obvious in view of Liu et al. and Pisanti et al. Therefore, the rejection of Claim 38, 42-43 under 35 U.S.C. §103(a) as allegedly unpatentable over Liu et al. in view of Pisanti et al. is overcome and withdrawal thereof is respectfully requested.

Claims 44-45 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Liu et al. in view of Pisanti et al. and further in view of Gold et al. (U.S. Patent No. 6,242,246).

The Examiner acknowledges that both the Liu et al. and Pisanti et al. references are silent respecting the use of solid support for immobilization of DNA for analysis. However, the Examiner alleges that Gold et al. teach an efficient and sensitive screening for DNA binding agents by immobilizing DNA on solid support and measuring the change of dye, e.g.,

fluorescence, indicative of the presence of a binding agent. The Examiner asserts that Gold et al. teach a variety of choices for solid support, including glass, polystyrene, gold or silicon.

Therefore, the Examiner alleges that it would have been obvious to one skilled in the art, at the time the invention was made, to combine the teachings of both Liu et al. and Pisanti et al. with that of Gold et al. The Examiner asserts that the use of solid support for immobilization of DNA for better efficiency is well known for increasing the sensitivity of an assay. The Examiner asserts that the methodology employed by Gold et al. is in an analogous field, e.g., measuring change of fluorescent dye as indicative of DNA binding agents.

As discussed above, Applicants respectfully submit that the combination of the teachings of Liu et al. and Pisanti et al. does not render the present invention obvious. Furthermore, Applicants submit that the reference to Gold et al. does not obviate the deficiencies of the references to Liu et al. and Pisanti et al. Thus, the Examiner has failed to establish a *prima facie* case of obviousness based on these references.

Therefore, the rejection of Claim 44-45 under 35 U.S.C. §103(a) as allegedly unpatentable over Liu et al. in view of Pisanti et al., and further in view of Gold et al., is overcome, and withdrawal thereof is respectfully requested.

In view of the foregoing remarks, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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anisms, unless a radical-forming step is reversible. A separate rate term may exist, however, of the form $k[\text{Cu}(\text{SO}_4)_a^{2-n}][\text{S}(\text{IV})]$. A similar Cu(II) term can contribute significantly to the slower sulfur(IV) reduction of chloroquoiron(III) complexes, in 1 M chloride media,³⁶ but was not observed in the sulfur(IV) reduction of sulfatoquoiron(III) complexes in sulfate media.⁶

Oxidation of sulfur(IV) by a pathway second order in sulfur(IV) is unusual. The previous observation of a second-order path, in the oxidation by chromium(VI), probably involves reaction between a sulfitechromate(VI) ester and a second sulfur(IV) species.³⁷ Mechanism 7 is similar to that proposed for the chromium system,³⁷ except for the structure of the intermediate; ester formation by FeL_3^{3+} does not appear possible. A mechanism analogous to 6 could not account for the exact form of the rate law in the chromium system,³⁷ $\text{rate} = k[\text{Cr}(\text{VI})][\text{S}(\text{IV})]^2[\text{H}^+]/(1 + a[\text{S}(\text{IV})])$, owing to the small value³⁸ of Q_{6a} .

Limiting mechanisms 6 and 7, representing approach to the transition state by two sulfur atoms, either in a single species (6), or separately (7), cannot be distinguished by the observations made in this study. The

(36) O. F. Zeck and D. W. Carlyle, unpublished results.

(37) G. P. Haight, Jr., E. Perchonock, F. Emmenegger, and G. Gordon, *J. Amer. Chem. Soc.*, **87**, 3835 (1965).

positive entropy of activation appears consistent with either mechanism. If mechanism 6 is correct, then comparatively great reactivity of $\text{S}_2\text{O}_3^{2-}$ in this system is implied; second-order terms could perhaps be found in other systems, including anion oxidants such as IrCl_6^{2-} , for which ion pairs or specific sulfur-ligand interactions are unlikely.

If mechanism 7 is correct, then one can question whether the species $(\text{FeL}_3 \cdot \text{S})^{\text{VII}}$ is only an ion pair or if a more specific interaction between inner- and outer-sphere ligands exists. An experimental approach to this question would include attempts to detect the complex, or other $\text{ML}_3 \cdot \text{S}$ complexes, and studies of reaction with other metal ion oxidants, especially highly charged ones. It has been suggested³⁸ that anion catalysis of the $\text{Fe}(\text{H}_2\text{O})_6^{2+} - \text{FeL}_3^{3+}$ reaction may involve specific interaction between a bridging anion and the phenanthroline ligand.

The unexpected results of this work are the suggestions that $\text{S}_2\text{O}_3^{2-}$, potentially a two- to four-electron reducing agent, may react rapidly in a one-electron step and an alternate possibility that decomposition of $(\text{FeL}_3 \cdot \text{S})^{\text{VII}}$ to FeL_3^{3+} and S(V) can be accelerated by S(IV).

(38) N. Sutin and A. Forman, *ibid.*, **93**, 5274 (1971).

Synthesis and Properties of Tetraaza[14]tetraene and Tetraaza[14]hexaene Macrocylic Complexes

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Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. Received November 1, 1971

Abstract: An efficient nontemplate synthesis of the new macrocycle 5,7,12,14-tetramethyl-1,4,8,11-tetraazacyclo-tetradeca-4,6,11,13-tetraene ($\text{H}_2(\text{MeHMe}(\text{en})_2)$, **11**) is described. This compound reacts with metal(II) acetates or with other metal(II) salts under conditions of nonaqueous chelation to afford the macrocyclic 12- π complexes $\text{M}(\text{MeHMe}(\text{en})_2)$ (**13**, $\text{M} = \text{Fe}(\text{II}), \text{Co}(\text{II}), \text{Ni}(\text{II}), \text{Cu}(\text{II}), \text{Zn}(\text{II})$), whose electronic properties are consistent with planar coordination. Treatment of the Ni(II) and Cu(II) complexes with 3 equiv of trityl tetrafluoroborate in acetonitrile results in oxidative dehydrogenation, yielding the 15- π cations $[\text{M}(\text{MeHMe-2,9-diene})]^+$ (**15**) which were isolated as their tetrafluoroborate salts. Conductivity, spectrophotometric, and epr results indicate that the nickel complex exists in a paramagnetic monomer \rightleftharpoons diamagnetic dimer equilibrium in solution. The nickel and copper cations are reduced by sodium borohydride in ethanol to the neutral 16- π complexes $\text{M}(\text{MeHMe-2,9-diene})$ (**14**). Voltammetric studies of these complexes in acetonitrile have established the existence of a three-membered electron-transfer series $14 (16-\pi) = 15 (15-\pi) = 16 (14-\pi)$. Members of the series are interconverted by reversible one-electron redox processes considered to alter the ligand oxidation level such that the terminal oxidized member, $[\text{M}(\text{MeHMe-2,8,10-triene})]^{2+}$ (**16**), contains a $(4n + 2)$ -stabilized ring system. 16- π Ni(II) complexes **26** derived from several recently reported dihydrooctaaza[14]annulene macrocycles have been prepared. These and the 16- π Ni(II) complexes **1** were found to undergo two-electron oxidations, presumably yielding the 14- π species **27** and **28**, respectively.

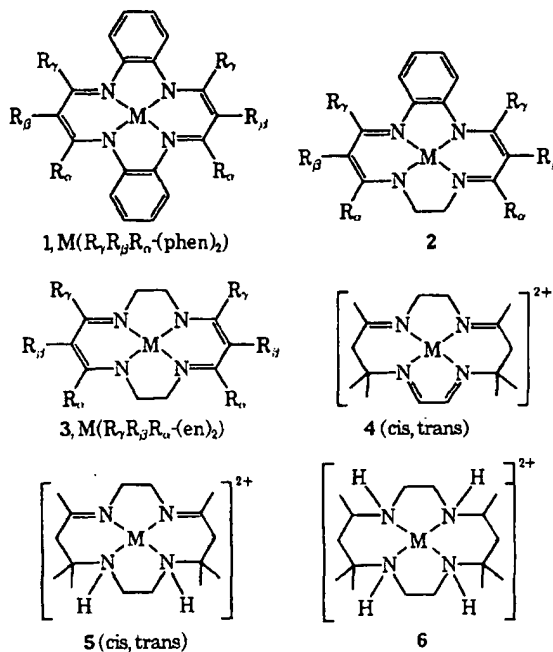
Attempts to relate electronic properties and reactivities of synthetic macrocyclic complexes to those of naturally occurring macrocycles, such as porphyrins and corrins, continue to promote considerable interest in their design and preparation. Work in this area has resulted in substantial progress in the development of cyclization reactions, usually involving metal ions, which have led to a variety of new macrocycles.¹ In

addition, development of systematic transformations, particularly hydrogenation and dehydrogenation reac-

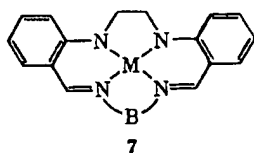
(1) (a) D. H. Busch, *Helv. Chim. Acta, Fasciculus Extraordinarius Alfred Werner*, 174 (1967); (b) D. H. Busch, K. Farmery, V. Goedken, V. Katovic, A. C. Melnyk, C. R. Sperati, and N. Tokel, *Advan. Chem. Ser.*, No. 100, 44 (1971); (c) J. P. Candlin, K. A. Taylor, and D. T. Thompson, "Reactions of Transition Metal Complexes," Elsevier, Amsterdam, 1968, pp 83-99; (d) L. F. Lindoy and D. H. Busch, *Prep. Inorg. React.*, **6**, 1 (1971).

tions, has allowed preparation of species with lesser or greater degrees of unsaturation than the precursor macrocyclic complex.

In contrast to the natural macrocycles, which usually contain four conjugated six-membered rings or three six- and one five-membered ring (6-6-6-6 and 6-6-6-5 types, respectively), the majority of synthetic macrocycles are of the 6-5-6-5 type.² Their complexes may be organized in terms of the degree of unsaturation of the ligand structure internal to the chelate rings. Known examples range from the completely conjugated 16- π electron system 1³⁻⁶ to the completely saturated system 6⁷ (and *C*-methyl derivatives thereof⁸) and include the 14- π ⁹ (2), 12- π ⁹⁻¹¹ (3), 8- π ^{8,12} (4), and 4- π ^{8,13,14} (5) systems. Cis and trans 6- π and 2- π com-



plexes derived from 5 have also been reported.^{8,12a} In addition, the neutral complexes 7 with $B = \text{phen}$



(2) Some 6-5-5-5 systems have been recently synthesized: S. C. Cummings and R. E. Sievers, *J. Amer. Chem. Soc.*, **92**, 215 (1970); *Inorg. Chem.*, **9**, 1131 (1970).

(3) E.-G. Jäger, *Z. Chem.*, **4**, 437 (1964).

(4) H. Hiller, P. Dimroth, and H. Pfitzner, *Justus Liebig's Ann. Chem.*, **717**, 137 (1968).

(5) P. Chave and C. L. Honeybourne, *Chem. Commun.*, 279 (1969).

(6) E.-G. Jäger, *Z. Anorg. Allg. Chem.*, **364**, 177 (1969).

(7) B. Bosnich, M. L. Tobe, and G. A. Webb, *Inorg. Chem.*, **4**, 1109 (1965).

(8) N. F. Curtis, *Coord. Chem. Rev.*, **3**, 3 (1968).

(9) E.-G. Jäger, *Z. Chem.*, **8**, 30, 470 (1968).

(10) E.-G. Jäger, *ibid.*, **8**, 392 (1968).

(11) P. Bamfield, *J. Chem. Soc. A*, 2021 (1969).

(12) (a) N. F. Curtis, *Chem. Commun.*, 881 (1966); *J. Chem. Soc. A*, 2834 (1971); (b) I. E. Maxwell and M. F. Bailey, *Chem. Commun.*, 883 (1966); (c) V. L. Goedken and D. H. Busch, *Inorg. Chem.*, **10**, 2679 (1971).

(13) L. G. Warner, N. J. Rose, and D. H. Busch, *J. Amer. Chem. Soc.*, **90**, 6938 (1968).

(14) J. M. Palmer, E. Papaconstantinou, and J. F. Endicott, *Inorg. Chem.*, **8**, 1516 (1969).

and en, which have been prepared recently,¹⁶ may be recognized as 14- π and 12- π cases, respectively.

In the course of our examination of electronic properties and chemical reactivities of divalent metal ions in planar or tetragonal N_4 environments, we have devised a nontemplate synthesis of the basic macrocycle 5,7,12,14-tetramethyl-1,4,8,11-tetraazacyclotetradeca-4,6,11,13-tetraene, $H_2(\text{MeHMe}(\text{en})_2)$, and its 12- π metal(II) complexes $M(\text{MeHMe}(\text{en})_2)$, $M = \text{Fe(II)-Zn(II)}$.

This report elaborates our recent account¹⁶ of this work and also describes a new synthetic approach to the dehydrogenation of coordinated ligands which has resulted in the preparation of Ni(II) and Cu(II) complexes of the new 16- π macrocycle ligand 5,7,12,14-tetramethyl-1,4,8,11-tetraazacyclotetradeca-2,4,6,9,11,13-hexaene. Spectral and limited magnetic properties are presented for the above complexes and several members of another new class of 16- π $M(\text{II})-N_4$ macrocyclic complexes derived from one type of recently reported dihydro-1,2,4,5,8,9,11,12-octaaza[14]annulenes.¹⁷ Electrochemical and synthetic studies have been carried out on a series of 16- π complexes in order to determine if they can be oxidized to the 14- π level. Species of the latter type would presumably contain a $(4n + 2)$ -stabilized macrocycle representing aza analogs of the carbocycle [14]annulene.¹⁸

Experimental Section

Preparation of Compounds. $\text{Ni}(\text{HHH}(\text{phen})_2)$, $\text{Ni}(\text{MeHH}(\text{phen})_2)$, and $\text{Ni}(\text{Me}, \text{COMe}, \text{H}(\text{phen})_2)$ were prepared by published methods.^{4,6} Analytical data for new compounds are given in Table I. Spectral and other properties are summarized in Tables II-V. Structural formulas are set out in Scheme I and in the text.

5,7,12,14-Tetramethyl-1,4,8,11-tetraazacyclotetradeca-4,6,11,12-tetraene, $H_2(\text{MeHMe}(\text{en})_2)$ (11) and Its Metal(II) Complexes, $M(\text{MeHMe}(\text{en})_2)$ (13). $H_2(\text{MeHMe}(\text{en})_2)$. To a solution of 30.0 g (0.30 mol) of 4-aminopent-3-en-2-one¹⁹ in 200 ml of dry dichloromethane was added 57.0 g (0.30 mol) of triethyloxonium tetrafluoroborate dissolved in 150 ml of dry dichloromethane. The solution was stirred at room temperature under an atmosphere of dry nitrogen for 30 min. Ethylenediamine (9.0 g, 0.15 mol), freshly distilled from sodium hydroxide, was added dropwise with stirring over a 30-min period. The solution was stirred for an additional 3 hr at room temperature during which time a white solid formed. Dichloromethane was removed under reduced pressure and replaced with 400 ml of absolute methanol. To this solution was added 16.2 g (0.30 mol) of sodium methoxide in 150 ml of methanol and thereafter an additional 9.0 g (0.15 mol) of ethylenediamine was immediately introduced. The reaction was allowed to proceed for 4 hr with stirring during which time ammonia was evolved. Removal of the methanol under reduced pressure, followed by extraction of the residue with hot absolute ethanol, yielded a first crop of cream-colored platelets from the cooled extract. A second crop was obtained by extraction of the residue with chloroform and removal of this solvent under reduced pressure. The two crops were combined and recrystallized from ca. 1800 ml of absolute ethanol to afford 13.0-13.2 g (35-35.5%) of pure product as cream-colored platelets. The product is best stored in a dry nitrogen atmosphere. Molecular weight: calcd, 248; found, 244 (osmometry, toluene solution). The mass spectrum revealed an intense parent ion peak at m/e 248.

(15) M. Green and P. A. Tasker, *Chem. Commun.*, 518 (1968); *Inorg. Chim. Acta*, **5**, 17, 65 (1971); D. St. C. Black and M. J. Lane, *Aust. J. Chem.*, **23**, 2039 (1970); E. Uhlemann and M. Plath, *Z. Chem.*, **9**, 234 (1969).

(16) T. J. Truex and R. H. Holm, *J. Amer. Chem. Soc.*, **93**, 285 (1971).

(17) (a) H. Neunhoffer and L. Motitschke, *Tetrahedron Lett.*, 655 (1970); (b) H. Neunhoffer, J. Stastny, and L. Motitschke, *ibid.*, 1601 (1971).

(18) F. Sondheimer, *Proc. Roy. Soc., Ser. A*, **297**, 173 (1967).

(19) R. D. Archer, *Inorg. Chem.*, **2**, 292 (1963).

Table I. Characterization Data for Macrocyclic Ligand and Complexes

Compound	Mp, °C	Calcd, %			Found, %		
		C	H	N	C	H	N
H ₂ (MeHMe(en) ₂)	226–228	67.70	9.74	22.56	67.83	9.70	22.65
[H ₂ (MeHMe(en))](BF ₄) ₂	175–180	36.22	6.08	14.08	36.34	6.05	13.68
Fe(MeHMe(en) ₂)	340–343	55.64	7.34	18.54	55.67	7.07	18.33
Co(MeHMe(en) ₂)	>360	55.08	7.26	18.35	54.63	7.06	18.24
Ni(MeHMe(en) ₂)	331–334	55.12	7.27	18.36	55.15	7.15	18.32
[Ni(H(MeHMe(en) ₂))](BF ₄)	247–251	42.69	6.04	14.22	43.15	6.03	14.31
[Ni(MeHMe-2,9-diene)](BF ₄) ^b	262–263	43.24	4.93	14.41	43.64	4.80	14.54
Ni(MeHMe-2,9-diene) dec	310–312	55.86	6.03	18.61	55.89	5.96	18.58
Ni(Me ₂ (ch)ooa)	273–275	49.90	5.76	29.10	50.08	5.93	29.29
Ni(Et ₂ (ch)ooa)	257–259	52.33	6.34	27.12	52.22	6.55	27.14
Cu(MeHMe(en) ₂)	298–299	54.26	7.16	18.08	54.29	7.09	18.18
[Cu(MeHMe-2,9-diene)](BF ₄)	255–256	42.81	4.62	14.26	43.25	4.83	14.41
Cu(MeHMe-2,9-diene)	320–322	54.98	5.93	18.31	55.08	6.10	18.31
Zn(MeHMe(en) ₂)	266–268	53.94	7.11	17.97	54.23	6.76	17.96

^a Sealed tube, uncorrected. ^b Calculated for [Ni(MeHMe-1-ene)](BF₄): C, 43.02; H, 5.41; N, 14.33.

Table II. Pmr Data for Macrocycles and Complexes

Compound	Solvent	Chemical shifts, ppm
H ₂ (MeHMe(en) ₂)	CDCl ₃	-1.95 (Me), -3.51 (CH ₂), -4.58 (CH), -11.6 ^a (NH)
[H ₂ (MeHMe(en))](BF ₄) ^b	py-d ₅	-2.36 ^c (Me), -3.83 ^d (CH ₂), -5.49 (CH), -8.80 ^a (NH)
Ni(MeHMe(en) ₂)	CDCl ₃	-1.90 (Me), -3.12 (CH ₂), -4.58 (CH)
[Ni(H(MeHMe(en) ₂))](BF ₄)	DMSO-d ₆	-2.01 (Me), -2.14 (Me), -3.40 ^d (CH ₂), -4.19 (CH), -4.92 (NH)
Zn(MeHMe(en) ₂) ^e	CHCl ₃	-1.97 (Me), -3.52 (CH ₂), -4.47 (CH)
H ₂ (Me ₂ (ch)ooa)	CDCl ₃	-1.65 ^d (β-CH ₂), -2.10 (Me), -2.32 ^d and -2.70 ^d (α-CH ₂), -17.4 (NH)
H ₂ (Et ₂ (ch)ooa)	CDCl ₃	-1.18 ^f (Me), -1.65 ^d (β-CH ₂), -2.30 ^d and -2.72 ^d (α-CH ₂), -2.50 ^f (CH ₂), -17.2 (NH)
Ni(Me ₂ (ch)ooa)	CDCl ₃	-1.67 ^d (β-CH ₂), -2.09 (Me), -2.50 ^d and -2.85 ^d (α-CH ₂)
Ni(Et ₂ (ch)ooa)	CDCl ₃	-1.13 ^f (Me), -1.70 ^d (β-CH ₂), -2.48 ^d and -2.88 ^d (α-CH ₂), -2.56 ^f (CH ₂)

^a Center of broad peak. ^b A second small peak in the (CH) region at -5.21 ppm (relative intensity ~10%) indicates the presence of a second conformation in solution or an impurity of similar structure. ^c Center of two overlapping singlets. ^d Center of a complex multiplet. ^e Spectrum taken in CHCl₃ because of loss of (CH) signal due to exchange in CDCl₃. ^f Centers of triplet and quartet of ethyl groups, J_{BH} = 7.5 Hz.

Table III. Magnetic and Electronic Spectral Data

Compound	μ _{eff} (BM) ^a	λ _{max} , cm ⁻¹ (ε) ^b
H ₂ (MeHMe(en) ₂) ^c		30,200 (sh, 5800), 32,600 (28,700), 33,100 (sh, 25,200)
Zn(MeHMe(en) ₂) ^c	dia	~18,500 (sh, 70), ~25,100 (sh, 1400), ~28,300 (sh, 10,100), 30,300 (17,000)
Fe(MeHMe(en) ₂) ^d	3.95	7690 (87), ~10,100 (sh, 140)
Co(MeHMe(en) ₂) ^d	2.06	10,870 (45), ~17,000 (sh, ~280), ~19,600 (sh, 790), ~21,500 (sh, 1290), ~23,200 (sh, ~1700), 25,800 (5230), ~27,800 (sh, 4200), 32,200 (7700), 37,500 (9130)
Ni(MeHMe(en) ₂) ^{c,e}	dia	17,900 (227), 21,500 (sh, 1200), 23,600 (sh, 3700), 24,950 (6090), ~30,400 (sh, ~4400), 34,500 (15,200), ~38,900 (sh, ~10,300)
[Ni(H(MeHMe(en) ₂))](BF ₄) ^c	dia	18,700 (186), 21,600 (sh, 140), ~24,400 (sh, ~550), 25,400 (sh, 1250), 28,100 (9930), 29,100 (sh, 8300), 36,300 (5060), 38,600 (6080)
[Ni(MeHMe-2,9-diene)](BF ₄) ^{c,f}	dia	7500 (565), 11,100 (2320), ~13,800 (sh, 1900), ~16,600 (sh, 1400), 18,800 (1740), ~21,700 (sh, 2600), ~23,500 (sh, 3200), 27,200 (12,400), 30,100 (11,100), 34,000 (23,100), 34,700 (sh, 22,100)
Ni(MeHMe-2,9-diene) ^{c,g}	dia	14,500 (195), 15,800 (175), ~17,300 (sh, 120), 21,100 (3620), 22,700 (3560), 27,500 (18,500), 28,700 (17,000), 33,100 (20,300), 36,800 (22,300)
H ₂ (Et ₂ (ch)ooa) ^c		31,100 (24,100), 39,500 (30,400)
Ni(Et ₂ (ch)ooa) ^c	dia	17,080 (3770), ~17,900 (sh, 3380), ~22,200 (sh, 5200), 22,700 (5730), 30,800 (12,300), ~37,900 (sh, 11,900)
Cu(MeHMe(en) ₂) ^{c,h}	1.78	16,200 (111), 20,900 (sh, 220), 22,500 (sh, 330), 24,700 (sh, 790), 27,700 (sh, 5900), 29,500 (21,800), 30,200 (sh, 13,000), 33,200 (10,300), ~40,000 (sh, ~12,500)
[Cu(MeHMe-2,9-diene)](BF ₄) ^c	1.11	12,740 (1890), ~14,820 (sh, 2190), 15,400 (2230), ~17,600 (sh, 1300), 21,600 (1110), ~23,100 (sh, 1380), ~27,500 (sh, 13,400), 29,200 (21,900), 32,100 (19,000), 33,800 (21,400), ~34,800 (sh, 19,500), 37,000 (17,600)
Cu(MeHMe-2,9-diene) ^{c,i}	1.78	15,100 (170), 16,600 (160), 21,000 (3240), 22,200 (3810), ~23,500 (sh, 2750), ~26,000 (sh, 5850), 28,700 (32,700), ~29,500 (sh, 29,600), ~33,500 (sh, 11,800), 35,400 (17,300), ~43,000 (sh, 28,000)

^a Solid state, ~25°C; dia = diamagnetic. ^b Apparent values, uncorrected for underlying absorption. ^c Chloroform solution. ^d DMF solution. Due to extreme air sensitivity of the Fe(II) complex, a reproducible spectrum at >10,500 cm⁻¹ was not obtained. ^e Methanol solution. ^f Acetonitrile solution. ^g Reproducible spectra were not obtained at <14,000 cm⁻¹ because of decomposition in ir lamp beam. ^h c = 9.5 × 10⁻⁴ M.

Table IV. Conductivity Data for Acetonitrile Solutions at 25°^a

Compound	Δ_0 ohm ⁻¹ cm ² equiv ⁻¹	κ	
		Calcd	Found
(<i>n</i> -Bu ₄ N)(BF ₄)	163	350 ^b	362
[Ni(H(MeHMe(en)) ₂)](BF ₄)	167	352 ^b	369
[Ni(MeHMe-2,9-diene)](BF ₄)	179	748 ^c	580
[Cu(MeHMe-2,9-diene)](BF ₄)	167	352 ^b	355

^a The cell was calibrated with 0.01 *N* KCl in distilled water. Measurements were made at four–six concentrations in the range 5×10^{-3} – 1×10^{-1} *M*. ^b Calcd for 1:1 electrolyte. ^c Calcd for 2:1 electrolyte. Value for 1:1 electrolyte is 362.

Table V. Polarographic Data for Nickel and Copper Complexes

Complex	Solvent	Couple ^a	$E_{1/2}$, V	i_d/C^b ($\mu A/mM$)	Slope, mV $E_{3/4} - E_{1/4}$
Ni(MeHMe-2,9-diene)	CH ₃ CN	0 \rightleftharpoons +1	+0.11	-29	64
		+1 \rightleftharpoons +2	+0.70	-24	54
[Ni(MeHMe-2,9-diene)](BF ₄)	CH ₃ CN	0 \rightleftharpoons +1	+0.10	33	59
		+1 \rightleftharpoons +2	+0.70	-26	52
Cu(MeHMe-2,9-diene)	CH ₃ CN	0 \rightleftharpoons +1	-0.04	-25	58
		+1 \rightleftharpoons +2	+0.50	-26	73
[Cu(MeHMe-2,9-diene)](BF ₄)	CH ₃ CN	0 \rightleftharpoons +1	-0.07	26	60
		+1 \rightleftharpoons +2	+0.50	-25	57
Ni(MeHMe(en)) ₂	DMF	0 \rightleftharpoons +1	+0.11	-14	64
Ni(MeHMe(NH) ₂) ₂	DMF	0 \rightleftharpoons +1	+0.18	-12	52
Cu(MeHMe(en)) ₂	DMF	0 \rightleftharpoons +1	+0.17	-15	61
Zn(MeHMe(en)) ₂	CH ₃ CN	0 \rightleftharpoons +1	+0.23	-22	86
Ni(MeHH(phen)) ₂	DMSO	-1 \rightleftharpoons 0	-1.63	7.0	61
		0 \rightleftharpoons +2	+0.58	-17	55
Ni(HHH(phen)) ₂	DMSO	-1 \rightleftharpoons 0	-1.66	8.0	64
		0 \rightleftharpoons +2 (?)	+0.65	-12	74
Ni(Me, COMe, H(phen)) ₂	CH ₃ CN	-1 \rightleftharpoons 0	-1.48	25	62
		0 \rightleftharpoons +1	+0.94	-24	68
Ni(Me ₂ (ch)ooa)	CH ₂ Cl ₂	+1 \rightleftharpoons +2	+1.14	-24	73
		-1 \rightleftharpoons 0	-1.20	25	57
Ni(Et ₂ (ch)ooa)	CH ₂ Cl ₂	0 \rightleftharpoons +2 ^c	+1.26	-43	71
		-1 \rightleftharpoons 0	-1.24	23	61
		0 \rightleftharpoons +2 ^c	+1.25	-40	65

^a Notation used indicates number of electrons transferred but does not necessarily imply strict electrochemical reversibility. ^b Comparison data for one-electron transfer: [Ni(tdt)₂]²⁻ = [Ni(tdt)₂]⁻ + e⁻, i_d/C ($\mu A/mM$) = 25 (CH₃CN); 12 (DMF); 6.8 (DMSO); 18 (CH₂Cl₂). ^c The total oxidation waves of these complexes appear to be comprised of two overlapping processes. The $E_{1/2}$ and slope values given are for the more anodic component and the i_d/C values are given for the total oxidative diffusion current. In each case, the less positive portion of the wave has a diffusion current of ca. $\leq 40\%$ of the total and appears to be markedly irreversible.

2,11-Diimonium-4,9-dimethyl-5,8-diazadodeca-3,9-diene Tetrafluoroborate (10). This compound was obtained by isolating the white solid formed during 3 hr of stirring as described in the preceding preparation. This material was collected by filtration under dry nitrogen and recrystallized from ca. 800 ml of absolute methanol to yield 18–20 g (31–35%) of pure product. No attempt was made to recover additional product from the filtrate. The product is hydrolytically unstable and should be handled under a dry nitrogen atmosphere.

H₂(MeHMe(en))₂ from 10 and Ethylenediamine. Sodium (0.46 g, 20 mmol) was dissolved in 100 ml of absolute methanol under a dry nitrogen atmosphere. To this solution was added 3.98 g (10 mmol) of 10 followed immediately by 0.60 g (10 mmol) of ethylenediamine. The reaction solution was stirred for 3 hr at room temperature while ammonia was evolved. Removal of methanol under reduced pressure followed by extraction of the residue with 200 ml of hot absolute ethanol and cooling of the extract solution yielded white crystals. Recrystallization from absolute ethanol afforded 1.3 g (52%) of crystalline product identified by melting point and pmr as H₂(MeHMe(en))₂.

M(MeHMe(en))₂, M = Fe(II), Co(II). These complexes were prepared by the nonaqueous chelation reaction in *tert*-butyl alcohol which has been described in detail previously.²⁰ Tetraalkylam-

monium tetrahalometalate(II) salts were employed as the anhydrous metal(II) source. Due to the slowness of the reactions at room temperature, they were conducted at 50° for 12–48 hr. At the conclusion of the reactions the solvent was removed under reduced pressure and the product extracted with and recrystallized from dry, degassed xylene under nitrogen atmosphere. The cobalt(II) complex was isolated as an orange-red crystalline solid which is apparently stable to dry air; it is air-sensitive in solution. The iron(II) complex was obtained as a brick-red solid which is sensitive to atmospheric oxygen in both solid and solution phases. Yields of the two purified complexes were ca. 50%.

M(MeHMe(en))₂, M = Ni(II), Cu(II). Reaction of hot ethanolic solutions containing equimolar proportions of H₂(MeHMe(en))₂ and the appropriate metal(II) acetate hydrate afforded the desired complexes in crystalline form. The nickel(II) complex was further

purified by recrystallization from dry xylene and was isolated as red-brown needles. The copper(II) complex was recrystallized under nitrogen from dry degassed xylene and was obtained as emerald green platelets. Yields of purified products were 80–95%.

Zn(MeHMe(en))₂. This complex was synthesized by nonaqueous chelation^{21,22} by utilizing *n*-butyllithium in tetrahydrofuran (distilled under a nitrogen atmosphere from lithium aluminum hydride). To a solution of 6 mmol of H₂(MeHMe(en))₂ in 200 ml of THF maintained at -20° was added 2 equiv of a 1.6 *M* *n*-butyllithium solution in *n*-hexane under a dry nitrogen atmosphere. Tetraethylammonium tetrachlorozincate(II) (6 mmol) was added and the reaction mixture stirred at room temperature for 6 days. Removal of the solvent under reduced pressure followed by extraction of the product with and recrystallization from dry degassed xylene yielded golden brown platelets in 65% yield. The product was dried *in vacuo* for 12 hr before analysis. The compound is sensitive to moisture and should be stored under a dry nitrogen atmosphere.

Dihydro-1,2,4,5,8,9,11,12-octaaza[14]annulenes, H₂(R₂(ch)₂ooa) and Their Nickel(II) Complexes, Ni(R₂(ch)₂ooa) (26). H₂(R₂(ch)₂ooa), R = Me, Et. Both of these compounds have been reported recently¹⁷ but preparative details were not given. The methyl derivative was obtained by the following method. 1,2-Cyclo-

(20) R. H. Holm, F. Röhrscheid, and G. W. Everett, Jr., *Inorg. Syn.*, 11, 72 (1968).

(21) W. R. McClellan and R. E. Benson, *J. Amer. Chem. Soc.*, 88, 5165 (1966).

(22) D. H. Gerlach and R. H. Holm, *ibid.*, 91, 3457 (1969).

hexanedione dihydrazone (2.5 g, 18 mmol) dissolved in 100 ml of absolute ethanol was added to a solution of 2.9 g (18 mmol) of triethyl orthoacetate in 50 ml of absolute ethanol containing 1 drop of concentrated sulfuric acid. The mixture was heated at ca. 60° for 24 hr under nitrogen. Red crystals appeared after 7 hr. The reaction mixture was cooled and the red crystalline product collected by filtration. After drying for 1 hr *in vacuo* 0.6 g (21%) of product was obtained. The ethyl derivative was prepared by an analogous procedure employing triethyl orthopropionate. A red crystalline product was obtained in 16% yield. The two compounds were identified by their melting points and pmr spectra.¹⁷

$\text{Ni}(\text{R}_2(\text{ch})_2\text{aaa})$, R = Me, Et. To a solution of 1.5 mmol of the free base in 175 ml of hot absolute ethanol was added 0.38 g (1.5 mmol) of nickel acetate tetrahydrate in 50 ml of hot absolute ethanol. The violet solid which separated was collected and air-dried. The complexes were purified by recrystallization from 1:1 v/v toluene-*n*-heptane and were isolated in 74–78% yield as violet crystals.

$[\text{Ni}(\text{H}(\text{MeHMe}(\text{en}))_2)](\text{BF}_4)$ (12). In attempts to prepare complexes derived from the neutral macrocycle 11, reactions of it and nickel(II) salts were carried out under several different conditions. Salts of the 1:1 type were obtained; the following procedure was the most reliable. $\text{H}_2(\text{MeHMe}(\text{en}))_2$ (3.0 g, 12 mmol) was dissolved in 100 ml of degassed absolute ethanol under a nitrogen atmosphere and 7.8 g (12 mmol) of tetraethylammonium tetrabromonickelate(II) in 100 ml of degassed absolute ethanol added. The reaction mixture was refluxed for 24 hr and filtered when hot in the absence of air. To the warm filtrate was added 2.7 g of sodium tetrafluoroborate in 50 ml of hot degassed methanol. Upon cooling red crystals separated. This material was purified by repeated (3–4 times) recrystallization from a degassed 1:1 v/v mixture of absolute methanol-ethanol under a nitrogen atmosphere. The product was obtained as deep red platelets (1.5 g, 31%), which should be protected from the atmosphere.

Reaction Products of Ni(MeHMe(en)). (a) $[\text{Ni}(\text{MeHMe-2,9-diene})](\text{BF}_4)$ (15, M = Ni). The following operations were carried out under a nitrogen atmosphere. To a solution of 4.0 g (13 mmol) of Ni(MeHMe(en)) in 30 ml of dry degassed acetonitrile was added 13.6 g (39 mmol + 5% excess) of trityl tetrafluoroborate.²³ The solution was heated at ~50° for 5 hr. During this time the solution became dark green and then dark green crystals separated. After cooling overnight a quantity of green-black crystals and a small amount of yellowish white crystals (triphenylmethane) were collected by filtration. The latter were removed by washing with degassed absolute ethanol. Purification was accomplished by two recrystallizations from ~450 ml of 1:1 v/v mixture of dry degassed acetonitrile-ethanol. The yield of green-black needles was 2.5 g (48%). The compound should be protected from the atmosphere.

(b) Ni(MeHMe-2,9-diene) (14, M = Ni). The following operations were carried out under a nitrogen atmosphere. $[\text{Ni}(\text{MeHMe-2,9-diene})](\text{BF}_4)$ (0.50 g, 1.3 mmol) was suspended in 25 ml of degassed absolute ethanol and 49 mg (1.3 mmol) of sodium borohydride was added. The mixture was stirred at room temperature for 4 hr. During the first 20 min, rapid gas evolution and a change in solution color from green to golden brown occurred. The microcrystalline solid which separated was collected and dried *in vacuo*. The pure complex was obtained by two recrystallizations from ca. 300 ml of dry degassed xylene (green solution) and isolated as copper-colored platelets, which were dried *in vacuo* overnight yielding 0.33 g (85%) of product.

Reaction Products of Cu(MeHMe(en)). (a) $[\text{Cu}(\text{MeHMe-2,9-diene})](\text{BF}_4)$ (15, M = Cu). The following operations were carried out under a nitrogen atmosphere. To a solution of 4.0 g (13 mmol) of Cu(MeHMe(en)) in 30 ml of dry degassed acetonitrile was added 13.6 g (39 mmol + 5% excess) of trityl tetrafluoroborate.²³ The mixture was stirred at ~50° for 8 hr. It turned dark red-brown almost immediately and after ca. 30 min, a dark green color developed and dark green crystals began to separate. At the end of the reaction period the mixture was cooled and filtered to yield large green-black crystals, which were washed with ~50 ml of absolute ethanol and twice recrystallized from 500 ml of a 1:1 v/v mixture of dry degassed acetonitrile-ethanol. Additional crops were isolated in both recrystallizations by reducing the volume of the filtrate. A total of 1.7–2.1 g (34–41%) of green-black crystals was obtained. The product should be protected from the atmosphere.

(b) Cu(MeHMe-2,9-diene) (14, M = Cu). The following operations were carried out under a nitrogen atmosphere. $[\text{Cu}(\text{MeHMe-2,9-diene})](\text{BF}_4)$ (0.40 g, 1.0 mmol) was suspended in 30 ml of degassed absolute ethanol and 39 mg (1.0 mmol) of sodium borohydride added. The mixture was stirred at room temperature for 6 hr. During the first 30 min, vigorous gas evolution took place and the crystals of the starting material were converted to a brown microcrystalline solid. The mixture was filtered and the brown solid collected was dried *in vacuo*. Three recrystallizations from ~300 ml of dry degassed xylene afforded 0.24 g (78%) of pure product as brown platelets, which were dried *in vacuo* at 80° for 3 days. The product should be protected from the atmosphere.

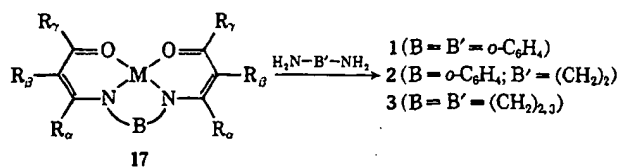
Physical Measurements. Electronic spectral data were obtained using a Cary Model 14 spectrophotometer. Magnetic measurements were made by the Faraday method using HgCo(NCS)₂ and Ni(en)₂S₂O₈ as calibrants. A Mechrolab Model 302 osmometer operating at 37° was used for molecular weight measurements in solutions prepared from dry toluene. A Princeton Applied Research Model 170 electrochemistry system was employed for electrochemical measurements. The usual polarographic measurements were carried out using a rotating platinum electrode as the working electrode. Solutions were ~10⁻³ M in complex and 0.10 M in tetra-*n*-butylammonium perchlorate as the supporting electrolyte in dichloromethane solution and 0.05 M tetra-*n*-butylammonium tetrafluoroborate as the supporting electrolyte in other solvents. All potentials were determined at 25° vs. a saturated calomel reference electrode. Pmr spectra were obtained on either a Varian HR-100 or a Hitachi Perkin-Elmer R-20B spectrometer using TMS as an internal standard. Conductivity measurements were made using as the solvent acetonitrile which had been distilled from calcium hydride under a nitrogen atmosphere and a Serfass conductivity bridge. Solutions were thermostated at 25.0 ± 0.2° during the measurements.

Mass Spectra. Low-resolution mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6D spectrometer operating at 70 eV. High-resolution mass spectra were determined using a CEC21-11B double-focusing spectrometer employing photoplate recording and operating at 70 eV. Tabulated below are the principal peaks in the parent ion region of the high-resolution spectra of Ni(MeHMe-2,9-diene) and Cu(MeHMe-2,9-diene). Given in the tabulation are the assigned isotopes and the observed and calculated exact masses for each. The following approximate masses together with the observed (calculated) relative intensities were obtained under low resolution in the parent ion region of Ni(MeHMe-2,9-diene): 300, 100 (100); 301, 19 (17); 302, 43 (40); 303, 9 (8); 304, 8 (6); 306, 2 (2).

Ni(MeHMe-2,9-diene)		
Ion ⁺	Obsd	Calcd
¹² C ₁₄ ¹ H ₁₈ ¹⁴ N ₄ ⁶³ Ni	300.0857	300.0884
¹² C ₁₃ ¹³ C ₁ ¹ H ₁₈ ¹⁴ N ₄ ⁶³ Ni	301.0901	301.0918
¹² C ₁₄ ¹ H ₁₈ ¹⁴ N ₄ ⁶⁰ Ni	302.0828	302.0863
¹² C ₁₄ ¹ H ₁₈ ¹⁴ N ₄ ⁶¹ Ni	303.0851	303.0841
¹² C ₁₄ ¹ H ₁₈ ¹⁴ N ₄ ⁶² Ni	304.0791	304.0814
¹² C ₁₄ ¹ H ₁₈ ¹⁴ N ₄ ⁶⁴ Ni	306.0799	306.0811
Cu(MeHMe-2,9-diene)		
Ion ⁺	Obsd	Calcd
¹² C ₁₄ ¹ H ₁₈ ¹⁴ N ₄ ⁶³ Cu	305.0806	305.0829
¹² C ₁₃ ¹³ C ₁ ¹ H ₁₈ ¹⁴ N ₄ ⁶³ Cu	306.0832	306.0863
¹² C ₁₄ ¹ H ₁₈ ¹⁴ N ₄ ⁶⁵ Cu	307.0826	307.0809
¹² C ₁₃ ¹³ C ₁ ¹ H ₁₈ ¹⁴ N ₄ ⁶⁵ Cu	308.0855	308.0843

Results and Discussion

Synthesis of Macrocycle and Complexes. Jager^{3,6,9,10} has demonstrated that macrocyclic complexes 1–3 can be prepared by reactions between the tetradentate β-ketoamine complexes 17 (M = Ni, Cu) and primary diamines. The occurrence or extent of reaction appears to be significantly dependent upon the nature of R_β. Cyclization reactions involving aliphatic diamines

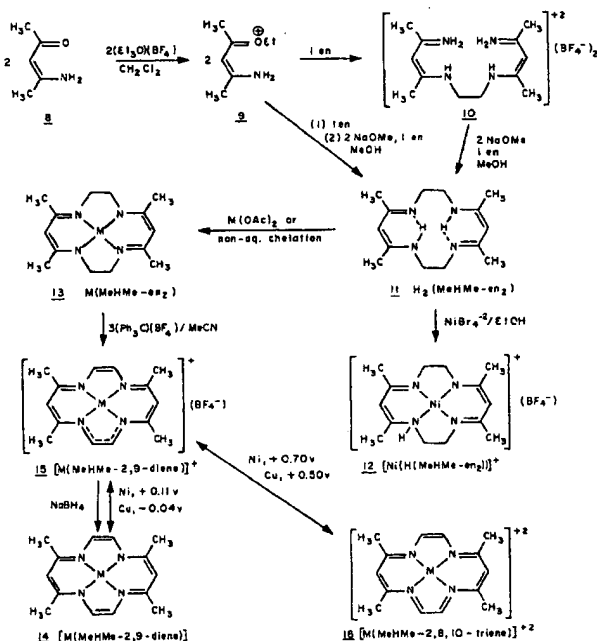


(23) H. J. Dauben, Jr., L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, 25, 1442 (1960).

fail unless $R_\beta = \text{COR}$ or COOR . For example, we have found that refluxing bis(acetylacetonate)ethylene-diamine-metal(II) complexes in neat ethylenediamine for up to 2 days did not result in cyclization. In related work Bamfield¹¹ has found that ring closure can be effected with analogs of 17 derived from 2-hydroxymethylenecyclohexa-1,3-dione but not from 2-hydroxymethylenecyclohexanone. Closure can be accomplished by reaction of *o*-phenylenediamine and 17 with or without carbonyl-containing groups at the β positions.⁶ In the latter case strongly forcing conditions are required. We have confirmed the synthesis⁶ of $\text{Ni}(\text{MeHH}(\text{phen})_2)$ using molten *o*-phenylenediamine as the reaction medium.

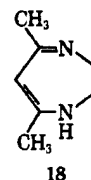
In view of the failure of the above template reactions to yield macrocyclic complexes lacking functional groups, a nontemplate method of synthesis was developed. The reactions employed are set out in Scheme I. Preparation of the macrocycle 5,7,12,14-tet-

Scheme I. Synthesis of the Macrocycle 11 and Its Derivative Ni and Cu Complexes.



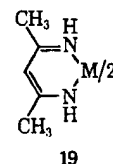
ramethyl-1,4,8,11-tetraazacyclotetradeca-4,6,11,13-tetraene ($\text{H}_2(\text{MeHMe}(\text{en})_2)$, 11) was first accomplished by a reaction sequence in which intermediates were not isolated. Alkylation of the β -ketoamine 8 yielded the *O*-ethyl cation 9, a dichloromethane solution of which was treated with 1 equiv of ethylenediamine and subsequently with 2 equiv of sodium methoxide and a second equivalent of diamine. Straightforward work-up afforded the pure macrocycle in 35% average yield. Molecular weight determination by osmometry in toluene solution and by mass spectrometry provides the necessary demonstration that the product is not the monomer 2,3-dihydro-5,7-dimethyl-1,4-diazepine²⁴ which has structure 18 in weakly polar media.²⁵ Ultraviolet and pmr spectral data (*cf.* Tables II and III) are consistent with those reported for noncyclic β -imino-

amines^{25b,26-28} and thus support structure 11. In particular the strongly deshielded resonance of the NH proton (-11.6 ppm) is indicative of the existence of hydrogen-bonded chelate rings. The course of the



reaction has been investigated by isolating the product formed from 9 and the first equivalent of ethylenediamine. The 1:2 salt 10 was obtained in 31-35% yield. The exact tautomeric structure of the cation is uncertain. Reaction of the salt with 2 equiv of base and 1 equiv of diamine gave the macrocycle 11 in 52% yield. These results indicate that the macrocycle is formed by two nucleophilic reactions. The first involves attack of the amine nucleophile at the $-\text{COEt}$ carbon of 9 and is analogous to similar reactions of alkylated β -ketoamine cations with amines and hydrosulfide ion to afford β -iminoamines²⁸ and β -aminothiones.²² The second reaction is an analogous nucleophilic attack on the neutral base obtained from 10, resulting in displacement of ammonia by the stronger base ethylenediamine and concomitant ring closure. No attempt has been made to isolate any products other than 11 which may have been formed in this reaction.

The neutral 12- π complexes $\text{M}(\text{MeHMe}(\text{en})_2)$ (13) are readily obtained from the macrocycle by reaction with the metal(II) acetate ($\text{Ni}(\text{II})$, $\text{Cu}(\text{II})$) or by non-aqueous chelation ($\text{Fe}(\text{II})$, $\text{Co}(\text{II})$, $\text{Zn}(\text{II})$). As a class they are moderately soluble in weakly polar solvents. The ligand structure requires an essentially planar $\text{M}-\text{N}_4$ geometry, although this stereochemistry is apparently preferred on an electronic basis inasmuch as McGeachin's sterically unencumbered bis(β -iminoamino) complexes 19 ($\text{M}(\text{MeHMe}(\text{NH})_2)_2$), $\text{M} = \text{Co}(\text{II})$, $\text{Ni}(\text{II})$, $\text{Cu}(\text{II})$, are planar in the solid and solution phases.²⁸ Magnetic and ligand field spectral



data for the $\text{M}(\text{MeHMe}(\text{en})_2)$ complexes of these metal ions (Table III) are closely comparable with those of types 2 and 3,⁹ 7¹⁵ ($\text{B} = \text{CH}_2\text{CH}_2$), and 19.²⁸ All $\text{Co}(\text{II})$ complexes are low spin and exhibit a d-d band near 11,000 cm^{-1} . The lowest energy ligand field transition occurs at 16,200 and 17,900 cm^{-1} for the spin doublet $\text{Cu}(\text{II})$ and diamagnetic $\text{Ni}(\text{II})$ complexes, respectively. $\text{Fe}(\text{MeHMe}(\text{en})_2)$ is of particular interest for it is one of the few well-characterized, apparently four-coordinate ferrous complexes. Its magnetic moment of 3.95 BM in the solid phase is consistent with an $S = 1$ ground state and finds analogy with the value (3.89 BM) at ambient temperature for $\text{Fe}(\text{II})$ phthal-

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(25) (a) H. A. Staab and F. Vögtle, *Chem. Ber.*, 98, 2701 (1965); (b) E. Daltrozzo and K. Feldman, *Ber. Bunsenges. Phys. Chem.*, 72, 1140 (1968).

(26) J. E. Parks and R. H. Holm, *Inorg. Chem.*, 7, 1408 (1968).

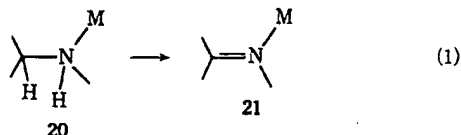
(27) C. L. Honeybourne and G. A. Webb, *Spectrochim. Acta, Part A*, 25, 1075 (1969).

(28) S. G. McGeachin, *Can. J. Chem.*, 46, 1903 (1968).

cyanine, whose electronic structure has been deduced to be $(xz,yz)^4(xy)^1(z^2)^1$ from magnetic anisotropy measurements.²⁹ Related measurements have not as yet been performed on $\text{Fe}(\text{MeHMe}(\text{en})_2)$ and its electronic ground state remains to be established. Both this complex and $\text{Co}(\text{MeHMe}(\text{en})_2)$ are markedly oxygen sensitive in solution and this behavior is currently under investigation.

Transformations of $\text{M}(\text{MeHMe}(\text{en})_2)$. One of our principal interests in macrocyclic tetraaza complexes of the 6-6-6-6, 6-6-6-5, and 6-5-6-5 types containing one or more saturated rings is concerned with their transformation into species whose conjugated ligand structures are related to those of natural macrocycles such as porphyrins and corrins. Although the 6-5-6-5 complexes **13** do not reproduce the ring-size patterns found in the biological ligands, they serve as feasible starting points for development of the desired reactions. These complexes lack the possibly interfering functional groups $\text{R}_\beta = \text{COR}, \text{COOR}$ present in **3**.^{3,6,9,10} Double dehydrogenations of each of their dimethylene bridges result in a fully conjugated and, hence, presumably stable 16- π ligand system. Such 16- π complexes, which have been obtained previously only as the di-*o*-phenylene bridged species **1**, have in addition the potentiality of generating a three-membered electron transfer series whose terminal oxidized member could have a 14- π ($4n + 2$) stabilized ligand structure.

The systematic transformation of a parent macrocyclic tetraaza complex into species with greater or lesser degrees of unsaturation was first achieved by Curtis.^{12a} By dehydrogenation and hydrogenation reactions he was able to transform the *cis*- and *trans*-tetraazadiene complexes **5** into their tetraazatetraene (**4**) and fully saturated analogs, respectively. This work,^{12a} together with other investigations,^{32-37a} has demonstrated that coordinated secondary amines^{37b} may be oxidatively dehydrogenated to imines (**20** \rightarrow **21**). A similar approach was attempted in this work.



Reaction of the macrocycle **11** with $\text{Ni}(\text{II})$ in the absence of base afforded, instead of the anticipated di-

(29) C. G. Barraclough, R. L. Martin, S. Mitra, and R. C. Sherwood, *J. Chem. Phys.*, **53**, 1643 (1970). There are few magnetic data reported for $\text{Fe}(\text{II})\text{-N}_4$ chelates. Moments of $\text{Fe}(\text{II})$ tetraphenylporphyrin have been claimed to be 0 BM³⁰ (benzonitrile solution) and 4.75 BM³¹ (solid) implying $S = 0$ and 2 in the two different phases. The only other $\text{Fe}(\text{II})$ complex with a moment similar to that of $\text{Fe}(\text{MeHMe}(\text{en})_2)$ is bis(monothioacetylacetonate)ethylenediimine- $\text{Fe}(\text{II})$ ³² (3.80 BM).

(30) A. Wolberg and J. Manassen, *J. Amer. Chem. Soc.*, **92**, 2982 (1970).

(31) H. Kobayashi, M. Shimizu, and I. Fujita, *Bull. Chem. Soc. Jap.*, **43**, 2335 (1970).

(32) D. M. C. Wei and S. C. Cummings, Abstracts of Papers, 162nd National Meeting of the American Chemical Society, Sept 1971, INOR-136.

(33) V. L. Goedken, Abstracts of Papers, 162nd National Meeting of the American Chemical Society, Sept 1971, INOR-150.

(34) E. Ochiai and D. H. Busch, *Inorg. Chem.*, **8**, 1798 (1969).

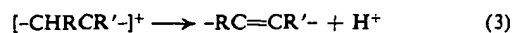
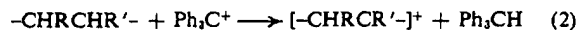
(35) E. K. Barefield and D. H. Busch, *ibid.*, **10**, 108 (1971).

(36) E. G. Vassian and R. K. Murmann, *ibid.*, **6**, 2043 (1967).

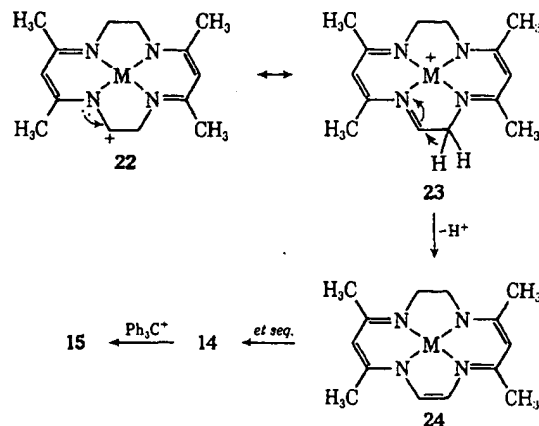
(37) (a) J. C. Dabrowiak, F. V. Lovecchio, V. L. Goedken, and D. H. Busch, Abstracts of Papers, 162nd National Meeting of the American Chemical Society, Sept 1971, INOR-140. (b) Recently the oxidative dehydrogenation of a coordinated primary amine has been reported: B. C. Lane, J. E. Lester, and F. Basolo, *Chem. Commun.*, 1618 (1971).

positive complex cation, the monoprotonated species **12** (Scheme I). Analytical results, nmr data (Table II), and conductivity in acetonitrile (Table IV) are consistent with the indicated formulation. Attempts to effect the conversion **20** \rightarrow **21** with several different oxidizing agents were not successful.

Attention was then directed to reactions involving loss of hydrogen, either as H^+ or H^- or both, from the five-membered rings of the complexes **13**, which do not contain coordinated secondary amines. The ultimately successful reactions were suggested by the work of Bonthron and Reid,³⁸ who found that additional conjugation could be introduced into certain unsaturated hydrocarbons by the reaction sequence 2 and 3. Hy-



dride abstraction by the strongly electrophilic trityl cation affords a resonance-stabilized carbonium ion which undergoes proton elimination resulting in the formation of a carbon-carbon double bond. As indicated in Scheme I, reaction of $\text{M}(\text{MeHMe}(\text{en})_2)$, $\text{M} = \text{Ni}(\text{II})$ and $\text{Cu}(\text{II})$, with 3 equiv of trityl tetrafluoroborate in acetonitrile effects dehydrogenation of the five-membered chelate rings. The overall process may be interpreted in terms of reactions 2 and 3, in which case the cation **22** \rightarrow **23** is initially formed and then eliminates a proton resulting in the species **24**. Repetition of the sequence would generate the fully con-



jugated complex **14**, which is oxidized to the cation **15** by the third equivalent of trityl cation.³⁹ The cationic species **15**, $[\text{M}(\text{MeHMe-2,9-diene})]^+$, were isolated in the form of their crystalline tetrafluoroborate salts. Upon treatment with sodium borohydride in ethanol, the cations were smoothly reduced to the corresponding neutral complexes **14**, $\text{M}(\text{MeHMe-2,9-diene})$, which were obtained in yields of ca. 80% after purification. The conversion of $\text{M}(\text{MeHMe}(\text{en})_2)$ (12- π) to $\text{M}(\text{MeHMe-2,9-diene})$ (16- π) is one of the few examples of

(38) W. Bonthron and D. H. Reid, *J. Chem. Soc.*, 2773 (1959).

(39) The individual steps **13** \rightarrow (**22**, **23**) \rightarrow **24** \rightarrow **14** are suggested by analogy to reactions 2 and 3;³⁸ studies of separate reaction steps have not been carried out. In particular, the proposed intermediate **24** has not been isolated. It is noted that the initial complexes **13**, like **14**, possess rather low polarographic half-wave potentials (Table V) and their oxidation by trityl cation could be the first step in the reaction sequence instead of hydride abstraction as shown. Reaction of **13** with 2 equiv of trityl tetrafluoroborate also afforded the cation **15** in ca. 30% yield. If the above sequence is correct, this result indicates that under the preparative conditions employed, the effective rate of oxidation of **14** is comparable to or exceeds the rate of hydride abstraction from **13** by trityl cation.

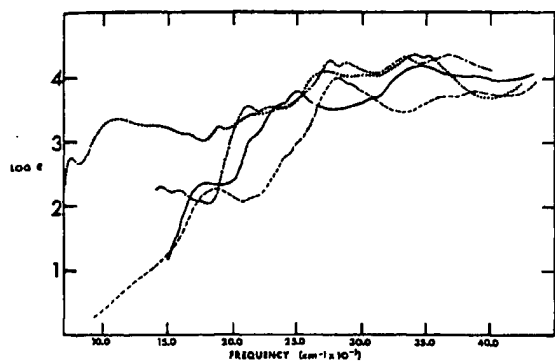
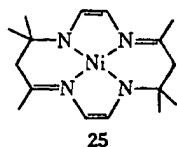


Figure 1. Electronic spectra of nickel complexes: (—) Ni(MeHMe(en)₂) (13) in chloroform; (---) [Ni(H(MeHMe(en)₂))]⁺(BF₄)⁻ (12) in methanol; (-·-·) Ni(MeHMe-2,9-diene) (14) in chloroform; (····) [Ni(MeHMe-2,9-diene)](BF₄) (15) in acetonitrile (9.5 × 10⁻⁴ M). Spectra of 13 and 14 could not be obtained below ca. 14,000 cm⁻¹ due to photolytic decomposition.

introduction of carbon-carbon unsaturation in chelate rings and is the only instance of formation of a fully conjugated ligand system by this means. Of the two previous examples,^{1b,36} the transformation of the dipositive *trans*-Ni(II) tetraene 4 under basic conditions to the corresponding neutral complex,^{1b} formulated here as the 12- π species 25, is the more closely related to the present work.



Properties of M(MeHMe-2,9-diene) and [M(MeHMe-2,9-diene)]⁺. Magnetic and electronic spectral results are given in Table III and Figures 1 and 2. The neutral macrocyclic complexes M(MeHMe-2,9-diene) were isolated as brown crystalline solids, which are only slightly soluble in weakly polar solvents yielding green solutions. Low solubility precluded determination of solution molecular weights and measurement of the pmr spectrum of the diamagnetic nickel complex. Confirmatory evidence for the formulation of these complexes as the fully conjugated 16- π species 14 has been obtained from their high-resolution mass spectra (*cf.* Experimental Section). The complexes are monomeric in the vapor phase and in each case the most intense spectral peaks are those of the molecular ions (¹²C₁₄¹H₁₈¹⁴N₄⁵⁸Ni and ¹²C₁₄¹H₁₈¹⁴N₄⁶³Cu). The nickel complex was also examined under low-resolution conditions and the observed and calculated relative intensities of isotope peaks in the molecular ion region were found to be in satisfactory agreement. The electrochemical studies described below reveal that the nickel and copper complexes 14 and 15 may be interconverted by reversible one-electron redox reactions, thereby demonstrating that these species differ only in total oxidation level. Electronic spectral comparisons of the complexes 13 and 14 of each metal reveal a number of differences, the most significant of which is the greater absorbance of the fully conjugated species in the near-infrared region.

The cationic complexes [M(MeHMe-2,9-diene)]⁺, 15, were obtained as green-black tetrafluoroborate

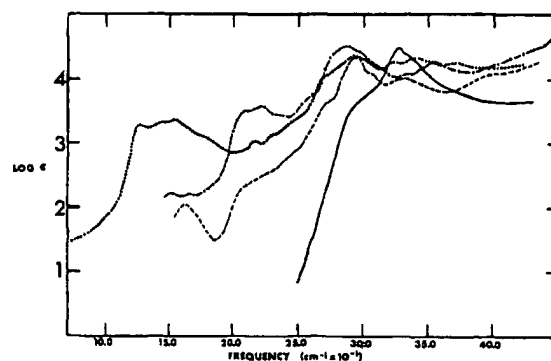


Figure 2. Electronic spectra of the macrocycle 11 and copper complexes: (—) H₂(MeHMe(en)₂) (11) in chloroform; (---) Cu(MeHMe(en)₂) (13) in chloroform; (-·-·) Cu(MeHMe-2,9-diene) (14) in chloroform; (····) [Cu(MeHMe-2,9-diene)](BF₄) in acetonitrile. Spectra of 13 and 14 could not be obtained below ca. 14,000 cm⁻¹ due to photolytic decomposition.

salts, which are moderately soluble in polar solvents such as acetonitrile, DMF, and DMSO, affording intense green solutions. Their electronic spectra are markedly different from the neutral species 14. Pronounced absorbance was found in the near-infrared, and no photochemical instability was detected. The origin of the magnetic moment of the solid copper complex (1.11 BM) is unknown at present and could result from intermolecular antiferromagnetic spin coupling or distribution over intramolecular spin singlet and triplet states. The most nearly analogous known complex, Cu(tetraphenylporphine)⁺, has a moment of 2.88 BM in solution,³⁰ indicating a triplet spin state. Solubility limitations prevented accurate magnetic measurements in solution. [Ni(MeHMe-2,9-diene)](BF₄) was found to be diamagnetic in the solid state at room temperature. Because the cation is an odd-electron species, this result implies spin pairing possibly through dimer or polymer formation in the solid state. The nature of this complex in solution was investigated by the conductivity and spectral measurements; solution magnetic studies could not be performed because of solubility restrictions.

The degree of association n of an electrolyte A _{n} B _{n} may be determined from measurement of the equivalent conductivity (Λ_e) as a function of concentration.⁴⁰ The slope A obtained from a plot of the Onsager limiting law $\Lambda_0 - \Lambda_e = A\sqrt{c}$ is characteristic of a particular n value in a given solvent. Conductivity data obtained from measurement of acetonitrile solutions (5 × 10⁻³–1 × 10⁻⁴ M) of three complexes prepared in this work and (*n*-Bu₄N)(BF₄) as a standard 1:1 electrolyte are given in Table IV. A comparison of calculated and observed A values⁴¹ reveals that tetra-

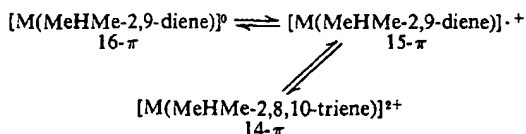
(40) R. D. Feltham and R. G. Hayter, *J. Chem. Soc.*, 4587 (1964).

(41) Values of Λ_0 were determined by extrapolation of plots of Λ_e vs. \sqrt{c} . The slopes A were obtained from these plots. Theoretical values of A were calculated for the electrolyte types (A⁺)(B⁻) (1:1) and (A₂²⁺)(B⁻)₂ (2:1) from the limiting law expression using constants appropriate to acetonitrile.⁴² In the calculation of A for the 2:1 case the equivalent ionic conductance λ_0^- of tetrafluoroborate in acetonitrile was taken as 108.5 ohm⁻¹ cm² equiv⁻¹⁴³ and λ_0^+ was determined by difference, $\Lambda_0 = \lambda_0^- + \lambda_0^+$. Solubility limitations prevented measurement of solutions of the complexes 15 with concentrations greater than ca. 5 × 10⁻³ M.

(42) P. Walden and E. J. Birr, *Z. Phys. Chem.*, 144, 269 (1929); J. F. Coetzee and G. P. Cunningham, *J. Amer. Chem. Soc.*, 87, 2529 (1965).
(43) H. L. Yeager and B. Kratochvil, *J. Phys. Chem.*, 73, 1963 (1969).

fluoroborate salts of the nickel complex **12** and the copper complex **15** behave as simple 1:1 electrolytes. The observed value of A for $[\text{Ni}(\text{MeHMe-2,9-diene})](\text{BF}_4)$ is, however, intermediate between the values calculated for 1:1 and 2:1 electrolytes found in this and other⁴⁴ conductivity studies in acetonitrile. Spectral studies of this compound in acetonitrile over the same concentration interval used in the conductivity measurements reveal definite departure from Beer's law and isosbestic points at 18,500 and 22,000 cm^{-1} . No spectral changes were observed at concentrations above $ca. 2.0 \times 10^{-3} M$. Similar spectral behavior is encountered in 3:1 v/v DMF-acetone solutions, whose epr spectra reveal a signal of $(g) = 2.002$, assigned to the spin-doublet monomer, with no resolved hyperfine splitting (peak-to-peak width 5.5 G). The spectrum of a frozen solution ($ca. -100^\circ$) consists of a single signal with no detectable anisotropy. From these preliminary results it is considered likely that $[\text{Ni}(\text{MeHMe-2,9-diene})]^+$ exists in a paramagnetic monomer \rightleftharpoons diamagnetic dimer equilibrium. Preliminary analysis indicates that the spectrum shown in Figure 1 corresponds to $ca. <10\%$ monomer present.

Polarographic Results. (a) $[\text{M}(\text{MeHMe-2,9-diene})]^z$ Complexes. Synthesis of the fully conjugated complexes **14** immediately raised the possibility that they would be subject to two one-electron oxidations, producing a heretofore unknown three-membered electron transfer series terminating in species with a $14-\pi$ ($4n+2$)-stabilized ligand system. The polarographic data in Table V and the cyclic voltammograms shown in Figure 3 indicate that the nickel and copper complexes each undergo two well-separated reversible or quasi-reversible one-electron oxidations in acetonitrile solution. Further, the cations **15** exhibit both a one-electron oxidation and a one-electron reduction at half-wave potentials within 30 mV of the corresponding processes of the neutral complexes.⁴⁵ Slopes of the polarographic waves of the cations correspond very closely to the theoretical value of 56 mV for a reversible one-electron transfer. No other waves were observed in the potential interval of $ca. -2.0$ to $+2.0$ V. These results lead to the formulation of the following three-membered electron transfer series (*cf.* Scheme 1) in which the redox processes are proposed to effect



changes in total oxidation levels of the macrocyclic ligands with the metals retaining a formal M(II) oxidation state. The epr data for the nickel cation de-

(44) A. L. Balch, I. G. Dance, and R. H. Holm, *J. Amer. Chem. Soc.*, **90**, 1139 (1968); A. Davison, D. V. Howe, and E. T. Shawl, *Inorg. Chem.*, **6**, 458 (1967).

(45) Cyclic voltammetric studies of $[\text{Ni}(\text{MeHMe-2,9-diene})](\text{BF}_4)$ in acetonitrile have established the reversibility of the oxidation and reduction processes of the cation. Polarographic wave slopes are then not consistent with a reversible two-electron transfer per dimeric unit. Diffusion currents given in Table V for this complex were calculated using monomeric formula weights. This procedure accords with the conductivity and spectrophotometric data if a rapid monomer \rightleftharpoons dimer equilibrium obtains and only the monomer is electroactive in the potential range employed. In other solvents and with different supporting electrolytes some evidence has been obtained for redox processes involving one-electron per dimeric unit. These processes are currently under investigation.

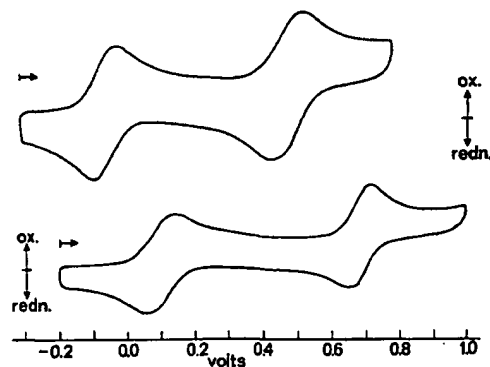


Figure 3. Cyclic voltammograms of the complexes **14** in acetonitrile: upper, $\text{Cu}(\text{MeHMe-2,9-diene})$; lower, $\text{Ni}(\text{MeHMe-2,9-diene})$. The voltammograms were recorded at a sweep rate of 0.50 V/sec using a stationary platinum electrode.

scribed above are consistent with a π -radical description. The dipositive cations **16** have not yet been isolated. In terms of previous considerations⁴⁶ the series is considered "complete" in that its limits are defined by the terminal reduced and oxidized forms of the ligand system in combination with a stable valence state of the metals employed. It is limited to three members rather than the five found for the similarly complete series $[\text{M}(\text{C}_6\text{H}_4(\text{NH}_2)_2)_2]^z$ ⁴⁶ and $[\text{Pt}(\text{R}_2\text{NCS-NNPh})_2]^z$ ⁴⁷ ($z = -2$ to $+2$), whose greater redox capacity arises from combinations of different oxidation states of separate ligands coordinated to the same metal.

The redox behavior of the complexes **14**, **15**, and **16** contrasts with that of Ni(II) and Cu(II) complexes of types **5** and **6**. The latter usually exhibit single-electron oxidation and reduction processes,⁴⁸ but these are characterized by potentials which are more anodic and much more cathodic than those which interrelate members of the above series. In these cases the ligands lack independent redox capacity and the processes may be reasonably interpreted as $\text{M}(\text{II}) \rightarrow \text{M}(\text{I})$ and $\text{M}(\text{II}) \rightarrow \text{M}(\text{III})$.⁴⁸

(b) Related $16-\pi$ Systems. In an attempt to assess the generality of the $16-\pi \rightleftharpoons 14-\pi$ electron transfer series, the polarographic behavior of two other systems related to the fully conjugated complexes **14** have been investigated. The octaaza[14]annulene complexes **26**⁴⁹ and the di-*o*-phenylene bridged complexes **1** potentially can be oxidized to the M(II) $14-\pi$ dication species **27** and **28**, respectively. Polarographic results for a

(46) A. L. Balch and R. H. Holm, *J. Amer. Chem. Soc.*, **88**, 5201 (1966).

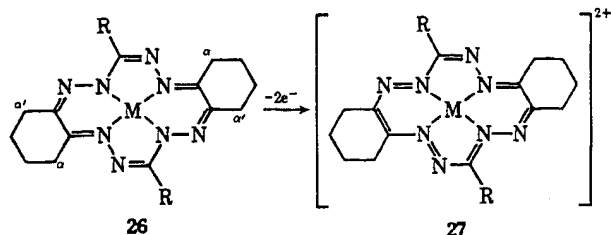
(47) C. E. Forbes, A. Gold, and R. H. Holm, *Inorg. Chem.*, **10**, 2479 (1971).

(48) (a) D. C. Olson and J. Vasilevskis, *ibid.*, **8**, 1611 (1969); (b) D. C. Olson and J. Vasilevskis, *ibid.*, **10**, 463 (1971); (c) D. P. Rillema, J. F. Endicott, and E. Papaconstantinou, *ibid.*, **10**, 1739 (1971). For related results of Cu(II) 6-6-5-5 tetraaza macrocycles, *cf.* L. F. Lindoy, N. E. Tokel, L. B. Anderson, and D. H. Busch, *J. Coord. Chem.*, **1**, 7 (1971).

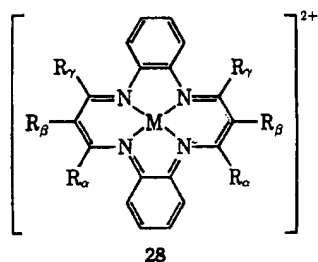
(49) In the initial report of the synthesis of metal-free octaazaannulenes,^{17a} a structure was proposed which, upon deprotonation, would afford neutral metal(II) complexes of D_{2h} symmetry. Pmr studies of a variety of these macrocycles and their Ni(II) complexes have established a C_{2h} structure,³⁰ as shown in **26**. The inequivalence of the α - and α' -methylene groups required by this structure but absent in the D_{2h} case is revealed by the pmr data in Table II for several free bases and their complexes. More recently the C_{2h} structure has been recognized,^{17b} but no supporting evidence for it was presented.

(50) J. E. Baldwin, R. H. Holm, R. E. Harper, J. Huff, S. Koch, and T. J. Truex, *Inorg. Nucl. Chem. Lett.*, **8**, 393 (1972).

number of Ni(II) complexes are given in Table V.



Anodic processes are observed in each case. With



the exception of Ni(Me, COMe, H(phen)₂) these processes correspond to apparent two-electron oxidations, most of which are at best quasi-reversible as judged by wave slopes. The results do imply that the oxidations 26 → 27 and 1 → 28, the possibility of which was recognized earlier by Jager,⁴ can be effected. No chemical oxidations of 1 and 26 have been attempted. Unlike 14 each of these complexes undergoes a one-electron reduction at potentials somewhat less negative than those required for the Ni(II) → Ni(I) reduction of species 5 and 6.

(c) M(MeHMe(en)₂) Complexes. For the purpose of comparison with the fully conjugated complexes 14, the polarographic behavior of M(MeHMe(en)₂), M =

Ni(II), Cu(II), and Zn(II), has been investigated. Results are given in Table V. These complexes do not reduce at potentials down to ca. -2.0 V but do undergo apparent one-electron oxidations at slightly positive potentials. No other anodic waves were observed. Due to the quite low potentials of these processes and their near-independence of metal ion, they are associated with oxidation of the ligand π system rather than with M(II) → M(III).⁴⁸ This interpretation is supported by the occurrence of similar slightly anodic oxidations with Ni(MeHMe(NH)₂)₂ (19, Table V) and [Ni(MeHMe(NCH₂CH₂NHMe)₂)]⁺,^{48a} which also contain delocalized β-iminoaminate chelate ring systems. The close correspondence of half-wave potentials between the oxidation of M(MeHMe(en)₂) and the first anodic process of M(MeHMe-2,9-diene) may indicate that they are related. In view of this, it should be emphasized that the representation 15 (Scheme I) for [M(MeHMe-2,9-diene)]⁺ is only one of a number of simple formulations depicting the delocalized nature of the 15-π ligand system.

Further examples of the nontemplate synthesis of tetraaza macrocycles and additional results dealing with the preparation, reactivity, solution behavior, and electronic properties of complexes of the types 14, 15, and 16 will be reported subsequently.

Acknowledgment. This research was supported by grants from the National Institutes of Health (GM-15471) and the National Science Foundation (GP-18978X). The high-resolution mass spectra were provided by the facility supported by National Institutes of Health Grant RR00317 (Professor K. Biemann, Principal Investigator) from the Biotechnology Resources Branch, Division of Research Resources. Useful discussions with Professor A. Davison are acknowledged.

Phosphonitrilic Compounds. XIV.¹ Basic Hydrolysis of Aryloxy- and Spiroarylenedioxycyclophosphazenes²

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Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. Received July 28, 1971

Abstract: Bis(aryloxy)cyclophosphazenes, [NP(OAr)₂]₃, and spirocyclic arylenedioxycyclophosphazenes, (NPO₂-Ar)₃, have been hydrolyzed in basic 25 vol % water in diglyme. For the bis(aryloxy) derivatives, the ease of hydrolytic removal of the first aryloxy group in [NP(OR)₂]₃ from phosphorus is in the order OR = *p*-NO₂C₆H₄O- > *m*-NO₂C₆H₄O- > *o*-NO₂C₆H₄O- >> C₆H₅O- > *p*-CH₃C₆H₄O-. For the spirocyclic derivatives, the rate of cleavage of the first aryloxy-phosphorus bond is in the order [NP(O₂C₆H₄-1,2)]₃ > [NP(O₂C₁₀H₆-2,3)]₃ >> [NP(O₂C₁₂H₆-2,2')]₃ and [NP(O₂C₁₂H₆-1,8)]₃. The mechanisms of these reactions are discussed, and comparisons are made with related phosphate ester hydrolyses.

Aryloxycyclo- and polyphosphazenes, [NP(OAr)₂]_{*n*}, and spirocyclic phosphazenes, [NP(O₂Ar)]₃ or [NP(O₂Ar)]₄, occupy an important place in phos-

phorus-nitrogen chemistry. Aryloxycyclophosphazenes, such as [NP(OAr)₂]₃ or [NP(OAr)₂]₄, are among the most thermally and oxidatively stable phosphorus

(1) Part XIII: H. R. Allcock, R. L. Kugel, and E. G. Stroh, *Inorg. Chem.*, **11**, 1120 (1972).

(2) Preliminary report of parts of this work have appeared: H. R.

Allcock and E. J. Walsh, *J. Amer. Chem. Soc.*, **91**, 3102 (1969); *Chem. Commun.*, 580 (1970).

Protonation and coordination properties towards Zn(II), Cd(II) and Hg(II) of a phenanthroline-containing macrocycle with an ethylamino pendant arm

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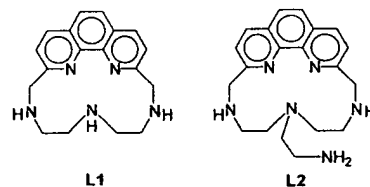
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Protonation and Zn(II), Cd(II) and Hg(II) coordination with the ligand 5-aminoethyl-2,5,8-triaza-[9]-10,23-phenanthrolinophane (L2), which contains an aminoethyl pendant attached to a phenanthroline-containing macrocycle, have been investigated by means of potentiometric, ¹H NMR and spectrofluorimetric titrations in aqueous solutions. The coordination properties of L2 are compared with those of the ligand 2,5,8-triaza-[9]-10,23-phenanthrolinophane (L1). Ligand protonation occurs on the aliphatic amine groups and does not involve directly the heteroaromatic nitrogens. The fluorescence emission properties of L2 are controlled by the protonation state of the benzylic nitrogens: when not protonated, their lone pairs are available for an electron transfer process to the excited phenanthroline, quenching the emission. As a consequence, the ligand is emissive only in the highly charged [H₃L2]³⁺ and [H₄L2]⁴⁺ species, where the benzylic nitrogens are protonated. Considering metal complexation, both [ML1]²⁺ and [ML2]²⁺ complexes (M = Zn(II) and Cd(II)) are not emissive, since the benzylic nitrogens are weakly involved in metal coordination, and, once again, they are available for quenching the fluorescence emission. Protonation of the L2 complexes to give [MHL2]³⁺ species, instead, leads to a recovery of the fluorescence emission. Complex protonation, in fact, occurs on the ethylamino group and gives a marked change of the coordination sphere of the metals, with a stronger involvement in metal coordination of the benzylic nitrogens; consequently, their lone pairs are not available for the process of emission quenching.

There is a continuing interest in the chemistry of polyaza-macrocycles because of their ability to form metal chelates in aqueous solutions and act as selective complexing agents for metal cations. Structural factors, such as ligand rigidity, electron-donor properties of the nitrogens and their disposition, have been shown to play significant roles in determining the binding features of macrocycles toward metal cations.^{1–13} Heteroaromatic subunits, such as 2,2'-dipyridine or 1,10-phenanthroline, are often introduced as integral parts of the host molecules.^{14–21} These units are rigid and provide two aromatic nitrogens whose unshared electron pairs act cooperatively in binding cations. At the same time, incorporation of these moieties into macrocyclic structures allows to combine within the same ligand the special complexation features of macrocycles with the photophysical and photochemical properties displayed by the metal complexes of these heterocycles.¹⁸ In this respect, these ligands are potential photochemical chemosensors for metals; they are able, in principle, to bind metal cations, and at the same time, to signal its presence in aqueous solution, due to energy- or photoinduced-electron transfer (PET) processes leading to enhancement of the fluorescence emission (CHEF effect) or enhancement of the emission quenching (CHEQ effect) of the heteroaromatic units upon metal coordination.

Earlier we reported on Zn(II) coordination to a series of phenanthroline-containing macrocycles composed by a polyamine chain connecting the 2,9-positions of a phenanthroline unit, such as the ligand 2,5,8-triaza-[9]-10,23-phenanthrolinophane (L1 in Scheme 1).^{19c,e} These ligands are able to give stable Zn(II) complexes in aqueous solution. Although the Zn(II) complexes with phenanthroline-based ligands generally display a marked CHEF effect upon Zn(II) binding, the Zn(II) complexes with these polyamine macrocycles are surprisingly not



Scheme 1

emissive: this effect was attributed to the benzylic amine groups, whose lone pairs are weakly involved in metal coordination and, therefore, available for an electron transfer process. This leads to a consequent quenching of the fluorescence emission of phenanthroline.^{19c,e}

We have now extended this study to the ligand 5-aminoethyl-2,5,8-triaza-[9]-10,23-phenanthrolinophane (L2), which displays an ethylamino group as a pendant arm attached to the macrocyclic framework of L1. It has been shown, in fact, that the attachment of an aminoalkyl side arm can strongly affect the coordination properties of the ligand^{22–34} as well as the photophysical properties of its complexes.^{13,35,36}

To further elucidate the role of metal cations in the fluorescence emissions properties of the complexes, we have also investigated the coordination properties of L1 and L2 toward the larger and softer Cd(II) and Hg(II) cations.

Results and discussion

Ligand protonation

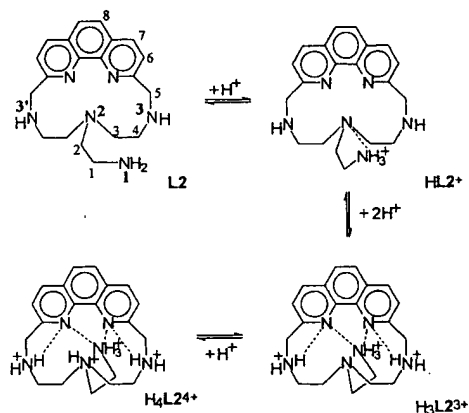
The protonation equilibria of L2 have been studied by means of potentiometric measurements in aqueous solutions and the

Table 1 Protonation constants of ligands L1 and L2 (NMe₄Cl 0.1 M, 298 K)

Equilibrium	log <i>K</i>	
	L1 ^a	L2
L + H ⁺ = LH ⁺	9.99	10.20(2) ^b
LH ⁺ + H ⁺ = LH ₂ ²⁺	7.72	8.78(4)
LH ₂ ²⁺ + H ⁺ = LH ₃ ³⁺	4.11	7.89(6)
LH ₃ ³⁺ + H ⁺ = LH ₄ ⁴⁺		2.57(6)

^a From ref. 19c. ^b This work; values in parenthesis are standard deviations on the last significant figure.

L2 basicity constants are reported in Table 1. The protonation constants of L1, previously determined,^{19c} are also reported for comparison. In the case of L1, it was found that all three protonation steps involve the aliphatic amine groups, while the phenanthroline unit remains unprotonated, even in the [H₃L1]³⁺ species, due to the by far lower basicity of phenanthroline nitrogens than aliphatic amine ones. A similar behaviour is also expected for L2. The data in Table 1 clearly show that the first three protonation constants are at least two log units higher than the protonation constant of 1,10-phenanthroline (log *K* = 4.96),³⁷ suggesting that these protonation steps occur on aliphatic amine groups. The low value of the fourth protonation constant does not allow, however, to infer hypothesis on the localisation of the fourth acidic proton. The protonation pattern of L2 has been clarified by recording ¹H NMR spectra at different pH values. The ¹H spectrum of L2 at pH 11.7, where the free amine predominates in solution displays five signals for the aliphatic protons and three for the aromatic ones, accounting for a C_{2v} time-averaged symmetry of the ligand, which is preserved over all the pH range investigated (2.5–11.7). The pH dependence of the ¹H NMR signals is reported in Fig. 1, together with the distribution diagram of the protonated species of L2. In the pH range 11.7–9.5, where the first proton binds to the ligand, the most significant changes in the ¹H spectra are the marked downfield shift of the signal of H1, in α-position with respect to N1; this strongly suggests that the first protonation step occurs on the NH₂ group of the pendant arm (Scheme 2).



The minor downfield shift observed for the protons H2 and H3, adjacent to N2, may suggest the presence of a hydrogen bond between the protonated N1 nitrogen and N2, and/or to a partial localisation of the acidic proton on the N2 tertiary nitrogen. Binding of the second and third proton to give the [H₃L2]³⁺ species occurs in the pH range 9.5–6 and produces a dramatic downfield shift of the signals of H4 and H5, in α-position with respect to the N3 and N3' benzylic nitrogens, indicating that these protonation steps involve the benzylic

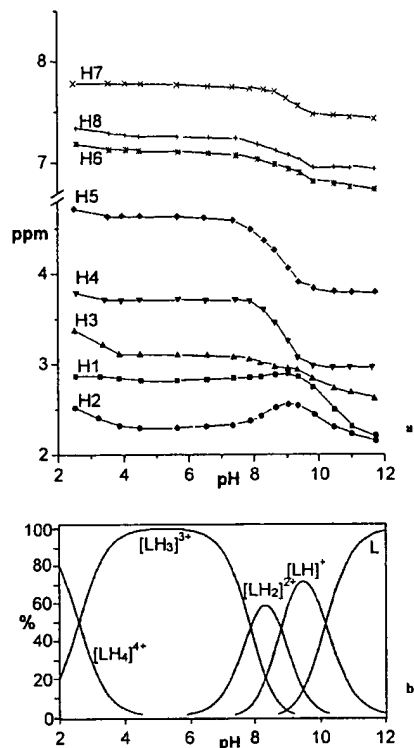


Fig. 1 pH dependence of the ¹H NMR signals of L2 (a) and distribution diagram of the L2 protonated forms (b) ([L2] = 1 × 10⁻³ M, I = 0.1 M).

nitrogens. At the same time, the resonance of H2 shifts upfield. These spectral features indicate that in the triprotonated form of the ligand the acidic protons are localised on the N1, N3 and N3' nitrogens, while N2 is not involved in proton binding. Such a disposition of the protons in the [H₃L2]³⁺ species would mean a minimum in electrostatic repulsion, since the protons occupy alternate positions, separated from each other by the unprotonated tertiary nitrogen N2 or by the phenanthroline unit. Actually, the downfield shifts of the resonances of protons H2 and H3 below pH 4 indicate that the fourth protonation step takes place on N2, adjacent to two already protonated amine groups, thus accounting for the low value of the fourth protonation constant. Interestingly, Fig. 1 also shows a downfield shift of the signals of the phenanthroline protons with the formation of the di- and triprotonated species of the ligand. Although these shifts are too small to be attributed to protonation of phenanthroline, this would indicate that the protonated aliphatic amine groups give hydrogen bond interactions with the heteroaromatic nitrogens. This hypothesis is confirmed by the analysis of the absorption spectra recorded on solutions containing L2 at various pH values. A slight red shift (5 nm) of the phenanthroline band at 273 nm, in fact, is observed from alkaline to strongly acidic pH values. Significant red shifts upon protonation have been reported,³⁸ instead, in the case of systems containing the chromophore 1,10-phenanthroline but not bearing amine groups. As shown in Fig. 2, a slight progressive increase of the absorbance at 268 nm is observed with the formation of the di-, tri- and tetraprotonated forms of the ligand, due to the formation of hydrogen bonds involving the phenanthroline nitrogens upon ligand protonation.

In contrast with absorption, the fluorescence emission intensity is very dependent on the protonation state of L2. A total quenching of the emission, in fact, is observed for the species L2, [HL2]⁺ and [H₂L2]²⁺, while [H₃L2]³⁺ and [H₄L2]⁴⁺ exhibit an intense emission (Fig. 2). As already observed in the case of ligand L1, the quenching effect in the less protonated species

Table 2 Selected bond lengths (Å) and angles (°) for the metal coordination environment in the $[\text{HgL1Br}]^+$ cation

Hg–N(1)	2.399(8)	Hg–N(4)	2.353(9)
Hg–N(2)	2.386(8)	Hg–N(5)	2.533(8)
Hg–N(3)	2.562(9)	Hg–Br	2.580(2)
N(1)–Hg–N(2)	69.2(3)	N(2)–Hg–Br	120.1(2)
N(1)–Hg–N(3)	135.3(3)	N(3)–Hg–N(4)	73.2(3)
N(1)–Hg–N(4)	111.9(3)	N(3)–Hg–N(5)	145.9(3)
N(1)–Hg–N(5)	68.0(3)	N(3)–Hg–Br	92.0(2)
N(1)–Hg–Br	121.0(2)	N(4)–Hg–N(5)	74.2(3)
N(2)–Hg–N(3)	68.0(3)	N(4)–Hg–Br	115.0(3)
N(2)–Hg–N(4)	111.8(3)	N(5)–Hg–Br	92.4(2)
N(2)–Hg–N(5)	135.5(3)		

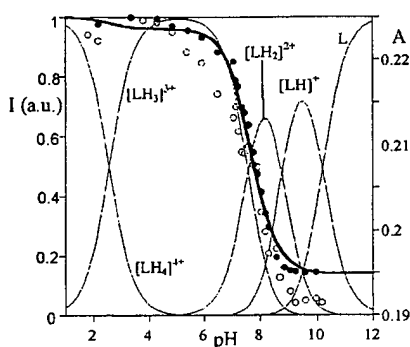


Fig. 2 pH Dependence of the absorbance at 268 nm (○, right y axis) and of the fluorescence emission intensity at 380 nm (●, left y axis, $\lambda_{\text{exc}} = 290$ nm) of L2 as a function of pH ($[\text{L2}] = 1.5 \times 10^{-5}$ M, 0.1 M NMe_4Cl , 298 K), superimposed to the distribution diagram of the protonated species of the ligand.

can be explained by an electron transfer process from the unprotonated amine groups closest to the excited phenanthroline, the benzylic nitrogens N3 and N3'.^{19c} As actually shown by the NMR study, in $[\text{H}_3\text{L}_2]^{3+}$ and $[\text{H}_4\text{L}_2]^{4+}$ both benzylic nitrogens are protonated. Their lone pairs are not available for quenching processes and, therefore, these highly protonated species are emissive.

Metal coordination

Crystal structure of $[\text{HgL1Br}]\text{ClO}_4$. The crystal structure consists of $[\text{HgL1Br}]^+$ complex cations (Fig. 3) and perchlorate anions. Selected bond angles and distances for the metal coordination environment are listed in Table 2. The Hg^{2+} ion is coordinated to the five donor atoms of the macrocycle and by an exogenous bromide anion. The coordination geometry can be best described as a strongly distorted octahedron, where the two heteroaromatic nitrogens (N(1) and N(2)) and the benzylic ones define the equatorial plane (maximum deviation 0.011(9) Å for N(1) and N(2)), while N(4) and the bromide anion occupy the apical positions. All the bond angles, however, strongly deviate from the theoretical values (Table 2). The metal ion lies 0.4133(6) Å above the equatorial plane, shifted toward the bromide ion.

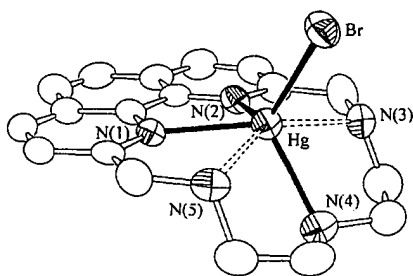


Fig. 3 ORTEP drawing of the $[\text{HgL1Br}]^+$ cation

Table 3 Stability constants of the Zn(II), Cd(II) and Hg(II) complexes with L1 and L2 (NMe_4Cl 0.1 M, 298 K)

Equilibrium	log K	
	L1	L2
$\text{L} + \text{Zn}^{2+} = \text{ZnL}^{2+}$	16.15 ^a	17.9(1) ^b
$\text{ZnL}^{2+} + \text{H}^+ = \text{ZnLH}^{3+}$		6.21(2)
$\text{ZnL}^{2+} + \text{OH}^- = \text{ZnL}(\text{OH})^+$	4.44	
$\text{ZnL}(\text{OH})^+ + \text{OH}^- = \text{ZnL}(\text{OH})_2$	2.75	
$\text{L} + \text{Cd}^{2+} = \text{CdL}^{2+}$	17.20(5) ^b	18.83(2) ^b
$\text{CdL}^{2+} + \text{H}^+ = \text{CdLH}^{3+}$		6.99(5)
$\text{CdL}^{2+} + \text{OH}^- = \text{CdL}(\text{OH})^+$	2.72(6)	
$\text{L} + \text{Hg}^{2+} = \text{HgL}^{2+}$		30.28(2) ^b
$\text{Hg}^{2+} + \text{L} + \text{Cl}^- = \text{HgClL}^+$	28.7(2) ^c	
$\text{HgL}^{2+} + \text{H}^+ + \text{Cl}^- = \text{HgClLH}^{3+}$		7.79(7)
$\text{HgClLH}^{3+} + \text{H}^+ + \text{Cl}^- = \text{HgCl}_2\text{LH}_2^{4+}$		4.49(9)

^a From ref. 19c. ^b This work, from potentiometric measurements. Values in parenthesis are standard deviations on the last significant figure. ^c From spectrofluorimetric measurements.

The data in Table 2, however, show that the two benzylic nitrogens N(3) and N(5) are bound at a larger distance than the two heteroaromatic donors and the central nitrogen N(4) of the aliphatic chain. In this respect, the phenanthroline nitrogens N(1) and N(2), N(4) and the bromide anion display a rather regular tetrahedral disposition around the Hg(II) ion. A similar disposition of the donors was also found in the crystal structure of the Zn(II) complex $[\text{ZnL1}(\text{H}_2\text{O})]^{2+}$.^{19c} In this complex, the metal is coordinated to the phenanthroline nitrogens, the central amine groups of the aliphatic chain and an exogenous water molecule in a resulting tetrahedral geometry, while the benzylic nitrogens are located *ca.* 2.5 Å apart from the metal. As in $[\text{ZnL1}(\text{H}_2\text{O})]^{2+}$, the overall conformation of the macrocyclic ligand in $[\text{HgL1Br}]^+$ is folded along the axis connecting the benzylic nitrogens, with a dihedral angle of 61.0(3)° between the mean planes defined, respectively, by the benzylic nitrogens and the aromatic unit and by the three secondary nitrogens of the aliphatic chains.

The crystal packing of $[\text{HgL1Br}]\text{ClO}_4$ displays pairs of symmetry related $[\text{HgL1Br}]^+$ cations interacting through face-to-face π -stacking between the two phenanthroline units (interplanar distance 3.57(1) Å). These dimeric units are associated *via* face-to-face π -stacking interactions between phenanthroline units belonging to two different pairs of cations (interplanar distance 3.60(1) Å) into pillars growing up along the *a* axis.

Zn(II), Cd(II) and Hg(II) complexation in aqueous solutions. Zn(II), Cd(II) and Hg(II) complexation with ligands L1 and L2 was studied by means of potentiometric measurements and the stability constants of the complexes formed in aqueous solutions are listed in Table 3. The low solubility of the Hg(II) complexes with L1 does not allow a speciation study by using potentiometric measurements in aqueous solutions. However, the formation constant of the Hg(II) complex could be determined by means of spectrofluorimetric measurements and its value is also reported in Table 3. In this case, a $[\text{HgL1Cl}]^+$ complex is formed in our ionic medium (NMe_4Cl), due to the high affinity of Hg(II) for the chloride anion.

Both ligands form stable complexes with the metal under investigation. Complex formation occurs at acidic pH values and, in the case of Zn(II) and Cd(II) complexation with L1, is followed by deprotonation of coordinated water molecules to give hydroxo-complexes at alkaline pH. In the case of Zn(II) complexation with L1, however, it was found that the benzylic nitrogens are only weakly involved in metal coordination.^{19c} The rigidity of the phenanthroline unit, in fact, stiffens the macrocyclic structure, precluding the simultaneous participation of all amine nitrogens in Zn(II) coordination. Actually,

the stability constants of the complexes with L1 are generally lower than the corresponding constants with the pentadentate macrocyclic ligand 1,4,7,10,13-pentaazacyclopentadecane (L3), where an ethylenediamine unit replaces the phenanthroline moiety of L1 (for instance, $\log K = 16.15$ for $[\text{CdL1}]^{2+}$ vs. $\log K = 19.2$ for $[\text{CdL3}]^{2+}$).³⁹ In the case of the $[\text{ML3}]^{2+}$ complexes all five donors are involved in metal coordination. On the other hand, 1,10-phenanthroline and the aliphatic amine *N,N'*-dimethylethylenediamine show similar binding ability toward Zn(II) and Cd(II) ($\log K = 6.55$ ⁴⁰ and 5.47 ⁴¹ for the equilibrium $\text{Zn}^{2+} + \text{L} = [\text{ZnL}]^{2+}$ and $\log K = 4.9$ ⁴² and 5.2 ⁴³ for the equilibrium $\text{Cd}^{2+} + \text{L} = [\text{CdL}]^{2+}$ with $\text{L} = 1,10$ -phenanthroline and *N,N'*-dimethylethylenediamine, respectively), and, in the case of Hg(II), 1,10-phenanthroline forms much more stable complexes than *N,N'*-dimethylethylenediamine ($\log K = 19.65$ and 11.78 for Hg(II) complexation with 1,10-phenanthroline and *N,N'*-dimethylethylenediamine, respectively).⁴³ These considerations suggest that the lower stability of the L1 complexes cannot be simply ascribed to the different binding ability of phenanthroline with respect to an ethylenediamine chain, but it is probably due to the stiffened macrocyclic structure of L1, which does not allow all the nitrogen donors to form strong coordination bonds with the metal ions. This suggestion is supported by the crystal structure of the $[\text{HgL1Br}]^+$ cation, which shows a distorted octahedral coordination environment for the Hg(II) ion, with both the benzylic amine groups coordinated at a longer distance than the remaining nitrogen donors.

These structural characteristics strongly affect the fluorescence emission features of the complexes.

Similarly to Zn(II), Cd(II) coordination usually gives a marked CHEF effect, *i.e.*, an increase of the fluorescence emission upon metal coordination. In principle, coordination of Cd(II) to the amine nitrogens should prevent the electron transfer quenching process, merely by coulombic effects.⁴⁴ In the present case, instead, the formation of the $[\text{CdL1}]^{2+}$ complex gives rise to a quenching of the fluorescence emission of phenanthroline. The absence of emission of the $[\text{CdL1}]^{2+}$ can be related to the weak involvement of the benzylic amine groups in metal coordination. These nitrogens are coplanar and close to the fluorophore, and therefore, in $[\text{CdL1}]^{2+}$ the lone pairs of the benzylic nitrogens can participate in an electron transfer process, quenching the fluorescence emission of the Cd(II) complex.

Similarly to Cd(II), the Hg(II) complex is also non-emissive. As shown in Fig. 4, the formation of this complex gives complete quenching of the fluorescence emission. In this case, however, the quenching process is due to the "heavy atom" effect of the Hg(II) cation.⁴⁵ The titration curve in Fig. 4 also allows to determine the stability constant of the Hg(II) complex with L1 ($\log K = 28.7$, Table 3)

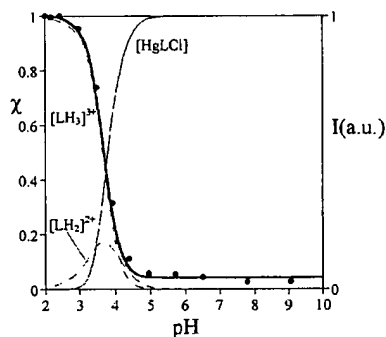


Fig. 4 Fluorescence emission intensity at 380 nm (●, right y axis; $\lambda_{\text{exc}} = 290$ nm) and molar fractions (χ) of the protonated (---) and complexed species of L1 (—, left y axis) in the presence of Hg(II) (1 : 1 molar ratio) as a function of pH ($\lambda_{\text{exc}} = 290$ nm, $[\text{Hg(II)}] = [\text{L1}] = 1.76 \times 10^{-5}$ M, $I = 0.1$ M NMe_4Cl , 298 K).

Considering Zn(II), Cd(II) and Hg(II) complexation with L2, the data in Table 3 clearly shows that the insertion of an ethylamino side arm on the L1 cyclic framework leads to an increase of stability of the $[\text{ML}]^{2+}$ complexes, accompanied by a marked tendency to form monoprotonated $[\text{ML2H}]^{3+}$ complexes. Metal complexation takes place at acidic pH to give $[\text{ML2H}]^{3+}$ species, which are prevalent in aqueous solution up to pH 6–7, where deprotonation of the complexes affords the $[\text{ML2}]^{2+}$ complexes. In the case of Hg(II) complexation, protonation of the complex is accompanied by chloride binding, with the formation of $[\text{HgCl}_2\text{L2H}_2]^{2+}$ species. The higher stability displayed by the L2 complexes can be simply related to the involvement of the amino group of the pendant arm in metal coordination, as often observed in macrocyclic complexes bearing alkylamino functionalities.^{22–34} Differently from L1, the $[\text{ZnL2}]^{2+}$ and $[\text{CdL2}]^{2+}$ complexes do not form any hydroxo-complex, indicating that in the coordination sphere of the metal cations is more fulfilled by the donor atoms of the ligand than in the corresponding L1 complexes. At the same time, the fact that the L1 complexes do not display any tendency to form protonated complexes would suggest that protonation of the $[\text{ML2}]^{2+}$ species occurs on the primary amine group of the side arm. In the case of Hg(II), detachment of the ethylamino donor implies coordination of a chloride anion to give, in our experimental conditions (0.1 M NMe_4Cl), a $[\text{HgCl}_2\text{L2H}_2]^{2+}$ protonated complex, likely due to the high affinity of Hg(II) for the chloride anion. To confirm our hypothesis on proton localisation in the monoprotonated complexes, we decided to perform ^1H NMR titrations on the L2 complexes. Fig. 5 reports the pH dependence of the ^1H NMR signals of the Cd(II) complex with L2, compared with the distribution diagram of the Cd(II) complexes. The most interesting finding is the significant upfield shift of the signals of the ethylenic chain H1 and H2 of the ethylamino pendant arm observed upon protonation of $[\text{CdL2}]^{2+}$ to give the monoprotonated $[\text{CdL2H}]^{3+}$ species in the pH range 6–8. This strongly suggests that the formation of $[\text{CdL2H}]^{3+}$ implies detachment from the metal of the ethylamino group, due to protonation of the N1 primary amine function. In the same pH range, the resonances of the phenanthroline protons do not display any noticeable shift, while the signals of the methylene groups H4 and H5, adjacent to the benzylic nitrogens, display a significant downfield shift. This spectral feature would suggest an increased interaction of the benzylic nitrogens with the metal cation upon detachment of the alkylamino pendant, with the formation of stronger coordinative bonds, as sketched in Fig. 6. Similar changes in the ^1H NMR chemical shifts of aliphatic protons are also observed in the case of protonation of the $[\text{ZnL2}]^{2+}$ complex. The hypothesis of an enhanced involvement of the benzylic amine groups in metal coordination is in accord with the fluorescence emission titrations carried out on solutions containing L2 and Zn(II) or Cd(II) in 1 : 1 molar ratio. Fig. 7 shows that the $[\text{ML2}]^{2+}$ complexes ($\text{M} = \text{Zn(II)}$, Cd(II) and Hg(II)) are non-emissive. In the case of the Zn(II) and Cd(II) complexes, the fluorescence emission is recovered upon complex protonation to give the $[\text{ZnL2H}]^{3+}$ or $[\text{CdL2H}]^{3+}$ species. While the lack of emission of the $[\text{ZnL2}]^{2+}$ and $[\text{CdL2}]^{2+}$ complexes can be simply ascribed to an electron transfer process involving the weakly coordinated benzylic nitrogen, as already observed in the corresponding L1 complexes, the fluorescence emission observed for the monoprotonated species can be related to the enhanced interaction of the benzylic nitrogens in metal coordination, occurring upon protonation and detachment of the ethylamino group. In other words, in $[\text{ZnL2H}]^{3+}$ or $[\text{CdL2H}]^{3+}$ the lone pairs of the benzylic nitrogens are more strongly involved in metal binding and cannot participate in the electron transfer process responsible for the emission quenching.

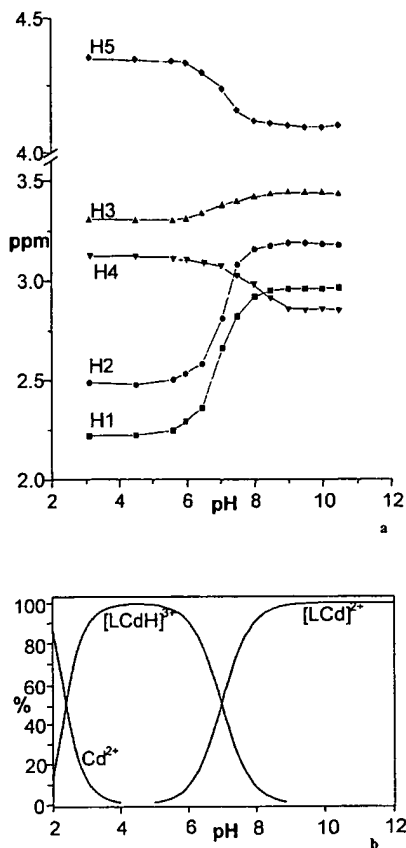


Fig. 5 pH Dependence of the ^1H NMR chemical shifts of the L2 complexes with Cd(II) (a) and distribution diagram for the system Cd(II)-L2 (b) ($[\text{Cd(II)}] = [\text{L2}] = 1 \times 10^{-3} \text{ M}$, $I = 0.1 \text{ M}$). The chemical shifts of the phenanthroline protons do not display significant changes in the pH range investigated and are not reported.

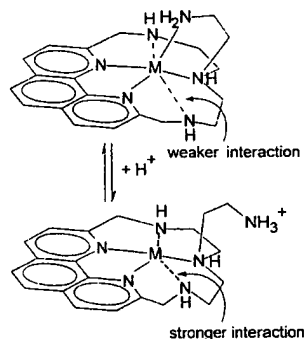


Fig. 6 Sketches of the proposed metal coordination environments in the $[\text{ML2}]^{2+}$ and $[\text{ML2H}]^{3+}$ complexes.

As already found in the case of L1, the Hg complex with L2 is non-emissive even in its protonated form, due to, once again, the "heavy atom" effect of the Hg(II) cation.⁴⁵

The Zn(II) and Cd(II) complexes with L2 are examples of systems whose fluorescence emission is controlled by the protonation state of the ligand, *i.e.*, by the pH of the medium. Although examples of similar pH-controlled fluorescent systems have been reported,^{13,35,36,46,47} most of them are constituted by a binding moiety for metals, such as a polyamine macrocycle, and a separated fluorophore pendant arm. In L2, instead, the binding unit and the fluorophore are gathered together within the same macrocyclic framework and the fluorescence emission is determined by the pH-controlled movement of a simple ethylamino side arm.

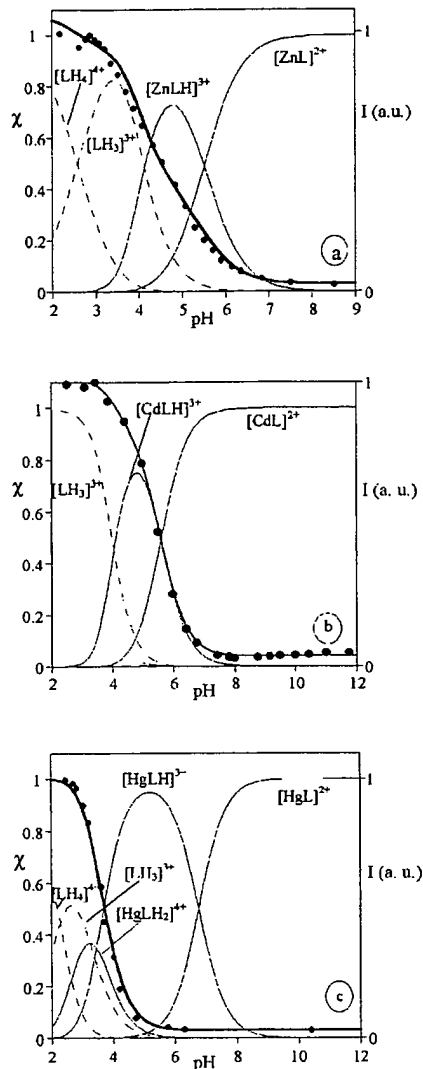


Fig. 7 Fluorescence emission intensity at 380 nm (\bullet , left y axis; $\lambda_{\text{exc}} = 290 \text{ nm}$) and molar fractions (χ) of the protonated (---) and complexed species of L2 (—, left y axis) in the presence of Zn(II) (a), Cd(II) (b) and Hg(II) (c) as a function of pH. ($[\text{M(II)}] = [\text{L2}] = 1.5 \times 10^{-5} \text{ M}$, $I = 0.1 \text{ M NMe}_4\text{Cl}$, 298 K).

Experimental

Synthesis

Ligands L1^{19c} and L2^{20c} were obtained as previously reported. Crystals of $[\text{HgL1Br}]\text{ClO}_4$ were obtained by slow evaporation at room temperature of an aqueous solution containing ligand L1 and HgBr_2 in equimolar ratio in the presence of an excess of NaClO_4 .

Potentiometric measurements

Equilibrium constants for L2 protonation and complexation reactions with L1 and L2 were determined by means of potentiometric measurements ($\text{pH} = -\log[\text{H}^+]$), carried out in $0.1 \text{ mol dm}^{-3} \text{ NMe}_4\text{Cl}$ at $298.1 \pm 0.1 \text{ K}$, in the pH range 2.5–11, by using the equipment that has been already described.⁴⁸ The reference electrode was an Ag/AgCl electrode in saturated KCl solution. The glass electrode was calibrated as a hydrogen concentration probe by titrating known amounts of HCl with CO_2 -free NaOH solutions and determining the equivalent point by Gran's method.⁴⁹ This allows one to determine the standard

potential E° , and the ionic product of water ($pK_w = 13.83 \pm 0.01$). $(1-2) \times 10^{-3} \text{ mol dm}^{-3}$ ligand and metal ion concentrations were employed in the potentiometric measurements. At least three measurements (about 100 experimental points for each system) were performed for each system. The computer program HYPERQUAD⁵⁰ was used to calculate the stability constants of metal complexes from emf data. In the case of Hg(II), the formation of ternary complexes with chloride was taken into account, by using the stability constants for the formation of Hg(II) chloro complexes from ref. 43. For all systems under investigation, the titration curves for each system were treated either as a single set or as separated entities without significant variations in the values of the protonation or metal complexation constants.

X-Ray structure analysis

Formula: $\text{C}_{18}\text{H}_{21}\text{BrClHgN}_5\text{O}_4$, monoclinic, space group $P2_1/n$, $M = 687.35$, $a = 8.315(5)$, $b = 23.272(5)$, $c = 11.159(1) \text{ \AA}$, $\beta = 96.53(2)^\circ$, $Z = 4$, $V = 2145(1) \text{ \AA}^3$, $T = 298 \text{ K}$, $F(000) = 1312$. Data collection: P4 SIEMENS X-ray diffractometer, $\lambda = 1.5418 \text{ \AA}$ (Cu-K α), graphite monochromated, $0.15 \times 0.1 \times 0.1 \text{ mm}$. 3540 Reflections collected ($\theta_{\text{max}} = 59.90^\circ$). The structure was solved by direct methods using the SIR-97 program.⁵¹ Refinement was performed by means of the full-matrix least squares method of the SHELX-97 program.⁵² All non hydrogen atoms were anisotropically refined. Hydrogen atoms were introduced in calculated positions and their coordinates and thermal factors were refined in agreement with the linked atoms. Refinement included 271 parameters on 2682 unique reflections. Final agreement factors were $R1 = 0.0396$ ($I > 2\sigma(I)$), $wR2 = 0.1018$ (all data).

CCDC reference number 225564.

See <http://www.rsc.org/suppdata/dt/b3/b315608/> for crystallographic data in CIF or other electronic format.

¹H NMR measurements

300.07 MHz ¹H spectra in D₂O solutions at different pH values were recorded at 298.1 K in a Varian Unity 300 MHz spectrometer. Peak positions are reported relative to HOD at 4.79 ppm. ¹H-¹H and ¹H-¹³C 2D correlation experiments were performed to assign the signals. In ¹H NMR titrations, the pD was adjusted by addition of small amounts of 0.1 mol dm⁻³ NaOD or DCl solutions to solutions containing the ligand alone or in the presence of equimolecular amounts of Zn(ClO₄)₂·6H₂O or Cd(ClO₄)₂·6H₂O. The ionic strength was 0.1 M NMe₄Cl. The pH was calculated from the measured pD values using eqn. (1):⁵³

$$\text{pH} = \text{pD} - 0.40 \quad (1)$$

Photophysical studies

All aqueous solutions were prepared in 0.1 mol dm⁻³ NMe₄Cl at 298.1 ± 0.1 K. HCl and NaOH were used to adjust the pH values that were measured on a Metrohm 713 pH meter. Absorption spectra were recorded on a Perkin-Elmer Lambda 6 spectrophotometer and fluorescence emission spectra on a Horiba-Jobin Yvon-Spex Fluorolog 3.22 spectrofluorimeter equipped with a ThermoNeslab RTE7 bath. All the fluorescence spectra were corrected for the instrumental response of the system. The formation constant of the Hg(II) complex with L1 was determined by least square fitting of the spectrofluorimetric data points derived from the titration carried out on the Hg(II)-L1 system.

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MEMORANDUM

DATE: May 3, 2007

TO: Technology Center Directors

FROM: *Margaret A. Focarino*
Margaret A. Focarino
Deputy Commissioner
for Patent Operations

SUBJECT: Supreme Court decision on *KSR Int'l. Co., v. Teleflex, Inc.*

The Supreme Court has issued its opinion in *KSR*, regarding the issue of obviousness under 35 U.S.C. § 103(a) when the claim recites a combination of elements of the prior art. *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007). A copy of the decision is available at <http://www.supremecourtus.gov/opinions/06pdf/04-1350.pdf>. The Office is studying the opinion and will issue guidance to the patent examining corps in view of the *KSR* decision in the near future. Until the guidance is issued, the following points should be noted:

- (1) The Court reaffirmed the *Graham* factors in the determination of obviousness under 35 U.S.C. § 103(a). The four factual inquiries under *Graham* are:
- (a) determining the scope and contents of the prior art;
 - (b) ascertaining the differences between the prior art and the claims in issue;
 - (c) resolving the level of ordinary skill in the pertinent art; and
 - (d) evaluating evidence of secondary consideration.

Graham v. John Deere, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

- (2) The Court did not totally reject the use of “teaching, suggestion, or motivation” as a factor in the obviousness analysis. Rather, the Court recognized that a showing of “teaching, suggestion, or motivation” to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

- (3) The Court rejected a rigid application of the “teaching, suggestion, or motivation” (TSM) test, which required a showing of some teaching, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the prior art elements in the manner claimed in the application or patent before holding the claimed subject matter to be obvious.

(4) The Court noted that the analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that it was “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements” in the manner claimed. The Court specifically stated:

Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an **apparent reason** to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis **should be made explicit**.

KSR, slip op. at 14 (emphasis added).

Therefore, in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.